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Editorial

FOR many years, this Journal has been published under the editorial direction of the American Heart Association. A succession of editors has been responsible for the excellent scientific standing which the Journal now enjoys and which reflects the great progress in cardiology in North America. In fact it would appear that this progress, both in volume and in scope, has outstripped the capacity of one journal. For this and other reasons, the Association has considered it in the way of wisdom to publish a journal of its own. We would take this opportunity of extending to the Association our best wishes for its success.

In the meantime, the American Heart Journal will continue to be published as in the past but under other direction and a new Editorial Board. It has been the custom of the publishers to give the Board complete authority and responsibility for the scientific content of the Journal. This custom will be continued.

In consideration of the wide field to which the study of the circulation extends, the Editorial Board hopes to plan its policy to meet a diverse clientele. In order that this may be accomplished, as many articles as possible will be included in each issue within the space available. This will, therefore, require that the articles should be written as concisely as is commensurate with clarity of description and concept. As in the past, illustrations will be welcomed, but they should not be redundant as this may sometimes lead to confusion, or at least can overshadow the principal points which require emphasis.

It will be our policy to publish as frequently as possible comprehensive but concise reviews of selected topics. These will be designed to bring the reader up to date by a reasoned exposition of the present status of the subject as it has developed over recent years.

We take this opportunity to express our thanks to the members of the new Editorial Board for their ready acceptance to serve. It is our hope that the advice and help asked of them will be neither an onerous nor an arduous burden. But without the confidence which they inspire we could not undertake our present task.

Editor

Original Communications

CARDIAC DISEASE IN PREGNANCY

A Study of the Patients With Heart Disease at the Philadelphia Lying-In Division of the Pennsylvania Hospital From 1937 to 1947, Inclusive

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THE study of heart disease in pregnancy is more complicated than in persons who do not have the extra strain of child-bearing. In addition to the increased difficulties of diagnosis due to the altered circulatory physiology in pregnancy, it is necessary to (a) estimate the patient's fitness for the pregnancy, (b) observe her closely through the prenatal period, (c) determine the proper time and the nature of an interruption of the pregnancy, if such is indicated, and (d) decide upon a safe method of delivery with the least additional strain to the patient.

The many studies on the physiological and pathologico-physiological aspects of pregnancy have not produced a satisfactory test to determine cardiac reserve. The inadequacy of laboratory studies plus the labile character of the cardiac status of many of these patients have forced cardiologists to resort to careful clinical studies of large series of patients to gain the necessary experience in handling these patients. We are interested, therefore, in analyzing our clinical experiences and the end results in the cardiac patients seen during an eleven-year period (1937-1947, inclusive) at the Pennsylvania Hospital.

THE MATERIAL AND METHOD OF STUDY

Through the courtesy of the Obstetrical and Gynecological Departments, the case records were reviewed on all pregnant women with any indication of heart disease who were admitted to the hospital during this eleven-year period. Slightly less than 30 per cent of this total number were found suitable for final analysis. All of the patients included were seen by a member of the Department of Cardiology in the prenatal cardiac clinic or on consultation in the hospital. In order to avoid, if possible, the inclusion of cases of pre-eclampsia and eclampsia, a diagnosis of hypertensive cardiovascular disease was made only when the patient had a past history of prolonged hypertension prior to pregnancy, and

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when daily studies of the blood pressure for at least one week postpartum showed a systolic level of 140 mm. Hg and a diastolic level of at least 85 mm. of mercury.

The functional capacities of all types of cardiac disease were classified according to the criteria for the classification and diagnosis of heart diseases of the New York Heart Association Criteria Committee.[1] In order to assure uniformity of the functional classes throughout this study, the older cases were reclassified, using the recently published standards.

One or more electrocardiograms were made on 84 per cent of these patients; orthodiagram, fluoroscopy, and six-foot film studies of the cardiac silhouette were made in 46 per cent. These methods of study, especially the roentgenological studies, were not often utilized on those patients hospitalized prior to 1940.

INCIDENCE OF CARDIAC DISEASE AMONG PREGNANT WOMEN

In the eleven-year period of this study, there was a total of 26,628 pregnant women delivered at the Pennsylvania Hospital. Of this total, 409 (1.5 per cent) were found to have heart disease of some type. An analysis of the various types of heart diseases seen in these 409 women is outlined in Table I.

TABLE I. THE ETIOLOGICAL TYPES OF HEART DISEASE AMONG 26,628 PREGNANT WOMEN

ETIOLOGY	NUMBER OF CASES
Rheumatic heart disease	324
Hypertensive cardiovascular disease	51
Congenital heart disease	18
Acute bacterial endocarditis	2
Syphilitic heart disease	1
Acute pericarditis	1
Arteriosclerotic heart disease (coronary artery occlusion)	1
Miscellaneous*	11
Total	409

*Paroxysmal auricular tachycardia, 6 cases. Hyperthyroidism, 3 cases. Hypothyroidism, 2 cases.

The incidence of cardiac cases among the pregnant women studied corresponds well with the 1.7 per cent and 1.8 per cent incidence given by Hamilton[2] and Hamilton and Thomson,[3] and is somewhat lower than the incidence of 2 to 3 per cent given by Stander[4] and by Stromme and Kuder.[5]

FUNCTIONAL CAPACITY AND DIGITALIS THERAPY

Sixty (14.6 per cent) of this series showed signs and symptoms of cardiac failure of various degrees when first seen. These patients were classified functionally as Class 3 or 4 and were promptly digitalized. Sixty-eight others, who

were originally classified functionally as Class 1 or 2, but showed increasing difficulty in going about their daily activities, were digitalized with beneficial results. Fifty-four per cent of the total of 128 digitalized patients began digitalis therapy two to six weeks prior to delivery. The remaining patients were digitalized at various times from several years before delivery to two or three days afterward.

The distribution of the patients in this series among the four functional classes and the number of patients in each class that were digitalized is shown in Table II.

TABLE II. THE DISTRIBUTION OF PATIENTS WITH HEART DISEASE AMONG THE FOUR FUNCTIONAL CLASSES

	CLASS 1	CLASS 2	CLASS 3	CLASS 4
Total number of cases (as originally classified)	206	143	46	14
Number of patients digitalized	3	65	46	14

The study shows that digitalis therapy has been employed quite freely in the management of these patients. It is our impression that it is an effective measure in lowering the incidence of sudden attacks of severe congestive heart failure in cardiac patients late in pregnancy, during labor, and in the early puerperium. The digitalis therapy was discontinued for many of the patients two to three weeks after delivery.

THE MATERNAL MORTALITY IN THE PREGNANT CARDIAC PATIENTS

The number of maternal deaths encountered in pregnant women, with or without cardiac disease, during this period of study is tabulated for comparison and analysis in Tables III and IV.

TABLE III. MATERNAL DEATHS RESULTING FROM CARDIAC AND NONCARDIAC CAUSES

Total number of pregnant women delivered in the hospital	26,628	
Total number of maternal deaths (cardiac and noncardiac)	46	
Maternal mortality (all causes)		0.17%
Maternal mortality of cardiac origin		0.05%

Ratio of maternal mortality of cardiac origin : noncardiac origin, 3 : 7.

TABLE IV. THE MATERNAL MORTALITY RATE OF PREGNANT PATIENTS WITH HEART DISEASE ACCORDING TO FUNCTIONAL CLASSES

Total number of cardiac cases studied		409
Total number of deaths among cardiac patients		14
(a) Number of deaths from the functional Classes 1 and 2	3	
(b) Number of deaths from the functional Classes 3 and 4	11	
Maternal mortality rate among pregnant cardiac patients		3.4%

The actual causes of death of the pregnant women with cardiac disease are summarized in Table V.

TABLE V. THE CAUSES OF DEATH AMONG 409 PREGNANT WOMEN WITH HEART DISEASE

CAUSES OF MATERNAL DEATH	NUMBER OF CASES
Acute congestive failure	5
Acute congestive failure with lobar or lobular pneumonia	4
Acute bacterial endocarditis	2
Acute congestive failure and rupture of the aorta	1
Acute exacerbation of rheumatic endocarditis	1
Pulmonary embolism	1
Total	14

Congestive heart failure was the main or contributory cause of death in ten of the fourteen patients (71 per cent). In seven of these ten patients the acute episode of congestive failure took place between the seventh and eighth months of gestation. The fact that most of the patients in failure were seen just prior to the eighth month of pregnancy lends support to the studies and experiences of Hamilton and Thomson,[2] Groedel,[6] Carr and Hamilton,[7] Semisch,[8] and others. These observers have noted that the circulatory load increased steadily from the third month to a maximum just before the last month of gestation. The other three patients began to show signs and symptoms of failure some hours after delivery. Death occurred in from six to forty hours after delivery with increasing dyspnea, cyanosis, and pulmonary edema. Although many investigators, including Hirst,[10] Hoffman and Jeffers,[11] and Hamilton and Thomson,[2] have noted that the first twenty-four to forty-eight hours post partum is the most dangerous period for patients with congestive heart failure, the real pathological physiology of this interesting clinical phenomenon is still not well understood.

It is also of note that various types of acute infections were responsible for seven of the fourteen deaths (50 per cent). The acute infection often precipitated acute congestive failure and in this manner, four of our patients died.

THE FETAL MORTALITY

There was a total of fifty-four fetal fatalities, constituting a mortality rate of 13.2 per cent. This includes fourteen therapeutic operative interruptions undertaken before the fourth month of pregnancy. The most common cause of death in this group of cases was prematurity. There were eight patients who died of heart failure before the delivery. Six post-mortem cesarean sections were done immediately after the death of the mother, but none were effective in obtaining a living infant.

The causes of fetal mortality as observed in these 409 cases are presented in Table VI.

TABLE VI. THE ETIOLOGICAL FACTORS CONCERNED WITH FETAL MORTALITY IN 409 PATIENTS WITH HEART DISEASE

CAUSES OF FETAL DEATH	NUMBER OF CASES
Prematurity	22
Undelivered (including 6 post-mortem cesarean sections)	8
Spontaneous abortions	6
Miscellaneous (pulmonary edema, atelectasis, acute bacterial endocarditis, and congenital heart disease)	17
Total Fetal Deaths	54

Equally high fetal mortality rates were reported by Clifford,[13] Teel,[14] and Hamilton and his associates,[2] among pregnant women with heart disease. They likewise found that prematurity was the most common single cause of these fatalities.

THE TYPES OF DELIVERY EMPLOYED

The various methods used for the termination of pregnancy and delivery of the fetus are tabulated in order of frequency in Table VII.

TABLE VII. THE METHODS UTILIZED FOR DELIVERY OR TERMINATION OF PREGNANCY IN 409 PATIENTS WITH HEART DISEASE

METHOD	NUMBER OF CASES
Low forceps	196
Spontaneous delivery	95
Cesarean section	74
Hysterotomy and evacuation	15
Breech extraction	9
Undelivered (including 6 post-mortem cesarean sections)	8
Spontaneous abortions	7
Dilatation and evacuation	5
Total	409

Table VII shows that nearly one-half of the total number of patients (47 per cent) were delivered by the use of low forceps at the second stage of labor to minimize the strain of delivery.

Table VIII presents the maternal and fetal mortality which occurred with each of the obstetrical procedures. The analysis is not intended to indicate the relative degree of safety of any particular method of delivery.

The record shows that pregnant cardiac patients in congestive failure during the latter months of pregnancy were treated conservatively. No major operative procedures were used in any one of the fourteen cases of maternal death, and over 60 per cent of the seventy-four cesarean sections done in this series were

TABLE VIII. A CORRELATION OF THE MATERNAL AND FETAL DEATHS WITH THE METHOD USED TO TERMINATE PREGNANCY

METHOD	MATERNAL DEATH	FETAL DEATH
Low forceps	3	3
Spontaneous delivery	2	15
Cesarean section	0	7
Hysterotomy and evacuation	0	11
Breech extraction	0	1
Spontaneous abortion	1	6
Undelivered (including 6 post-mortem cesarean sections)	8	8
Dilatation and evacuation	0	3
Totals	14	54

performed for gynecological reasons. There was not a single maternal death in a total of eighty-nine abdominal deliveries which included seventy-four cesarean sections and fifteen hysterotomies.

STERILIZATION OF PATIENTS SUFFERING FROM HEART DISEASE

A total of thirty sterilizations were performed in the 409 patients. In sixteen, hysterotomy or the sectioning of the Fallopian tubes was performed during cesarean section. In the remaining fourteen, sterilization was done from one month to one and one-half years after delivery. None of these patients developed any complication as a result of the operations.

ANESTHESIA

The types and frequency of anesthesia used in this series are listed in Table IX. Ether was the anesthesia most often used in patients admitted to the hospital before 1940. More recently, nitrous oxide or caudal and spinal anesthesias have been in general use. Since the employment of these methods was not strictly controlled, no conclusions can be drawn regarding the superiority of any one of these methods. It is our impression, however, that the proper use of anesthesia has an important place in lessening the strain of labor; and that caudal and spinal anesthesias may be safer for these patients than general anesthesia.

TABLE IX. THE TYPES OF ANESTHESIA UTILIZED IN THE DELIVERY OF 409 PATIENTS WITH HEART DISEASE

ANESTHESIA	NUMBER OF CASES
Spinal procaine	50
Caudal procaine	105
Nitrous oxide	80
Ether with or without nitrous oxide	166
Morphine and scopolamine	5
Demerol	3
Total	409

RHEUMATIC HEART DISEASE

It is estimated by different investigators that rheumatic heart disease complicates 1.6 to 2.6 per cent of all pregnancies, and constitutes the form of disease in 87 to 95 per cent of all of the pregnant patients suffering from heart disease.[2-5,15,16] Rheumatic heart disease was encountered 324 times in this series of 409 cases. A large majority of our cases (83 per cent) fell functionally into Classes 1 or 2 in the early months of gestation. All of these patients were considered satisfactory to carry on to full-term delivery. A similar distribution of cases in the functional classes was recorded by Stander[1] and others.[5,15,17]

It is generally believed that the age of the patient with rheumatic heart disease is an important factor in the development of congestive heart failure.[2,3,18,19] Bunium and Rubricus[20] have recently stressed the importance of the patient's position in the natural course of her rheumatic heart disease as an important factor in prognosticating heart failure and the risk involved in pregnancy. In our series 30.8 per cent of the patients with rheumatic heart disease were 30 years of age or older. Six of the twelve maternal deaths among the rheumatic heart disease cases occurred in this older age group. All six died of congestive heart failure.

Mitral valve disease alone was found in 83 per cent of the patients. Combined mitral and aortic valve lesions were present in 16.9 per cent of the patients. Thus, involvement of the mitral valve was present in almost 100 per cent of the patients. Seven deaths occurred in patients with mitral lesions alone, whereas five deaths occurred among the group with combined mitral and aortic valve disease. No conclusion can be drawn concerning the relationship of the mortality rate to the valvular involvement on the basis of these few cases.

Three patients with the complication of auricular fibrillation were seen in the seventh to the ninth week of their pregnancies. These patients were admitted to the hospital and promptly digitalized. Combined hysterotomy and sterilization was performed after the ventricular rate was well controlled. All recovered without complications.

The methods used in the delivery and termination of pregnancy in patients with rheumatic heart disease are listed in the order of frequency in Table X.

TABLE X. METHODS OF DELIVERY OR TERMINATION OF PREGNANCY UTILIZED IN 324 PATIENTS WITH RHEUMATIC HEART DISEASE

METHODS OF DELIVERY OR TERMINATION OF PREGNANCY	CLASS 1	CLASS 2	CLASS 3	CLASS 4	TOTAL
Low forceps	83	69	11	3	166
Spontaneous	35	28	10	1	74
Cesarean section	17	19	12	4	52
Hysterotomy and evacuation	0	3	7	0	10
Breech extraction	2	4	0	0	6
Spontaneous abortion	1	4	0	0	5
Dilatation and evacuation	0	4	0	0	4
Undelivered (including 6 cases of post-mortem cesarean sections)	0	0	3	4	7
Totals	138	131	43	12	324

As indicated in the table, over 50 per cent of the patients with rheumatic heart disease were delivered with the aid of low forceps during the second stage of labor. Of fifty-two cesarean sections performed on patients with rheumatic heart disease, twenty-four were done because of heart disease, as were seven of the ten hysterotomies. This constitutes approximately 9.5 per cent of the total deliveries in patients with rheumatic heart disease. Postoperative complications were encountered in three cases. These complications were: thrombophlebitis of the left femoral vein in one case; postoperative pneumonia in one case; and delayed union, with infection of the abdominal incision in one case. All three patients made a good recovery.

HYPERTENSIVE CARDIOVASCULAR DISEASE

Hypertensive cardiovascular disease was diagnosed in fifty-one patients, by means of the criteria mentioned previously. The patients in this group were older on the average than those studied in the rheumatic group. Thirty-two of the fifty-one patients were 30 years of age or older. Most of the hypertensive patients (49 of 51) were classified functionally in Class 1 or 2, and were satisfactory from the cardiac standpoint to withstand pregnancy and labor. The other two patients were placed in Class 3.

All of these pregnant hypertensive women exhibited a rising blood pressure with the maximum pressures occurring at the time of labor. Eight of them, in addition, had albuminuria, microscopic hematuria, and rise in blood urea nitrogen late in pregnancy. These changes were transitory and disappeared two to three weeks after the pregnancies were artifically or spontaneously terminated.

Reid,[21] Brown,[22] and Hamilton[2] and their associates have observed the tendency to acute exacerbation of the hypertensive state in these patients during pregnancy. It is the opinion of these authors and of several others[8,18,23] that following pregnancy, hypertension usually tends to increase, and that the life expectancy of these patients is shortened. The experience obtained through the study of this limited series, however, seems to agree with the contention of Chesley and his co-workers[24,25] that repeated pregnancies are not necessarily harmful to the hypertensive woman, if toxemia of pregnancy does not occur.

The methods used for delivery or termination of the pregnancy in patients with hypertensive cardiovascular disease are listed in Table XI.

TABLE XI. METHODS OF DELIVERY OR TERMINATION OF PREGNANCY IN FIFTY-ONE PATIENTS WITH HYPERTENSIVE CARDIOVASCULAR DISEASE

METHODS OF DELIVERY	NUMBER OF CASES
Low forceps	15
Spontaneous	13
Cesarean section	13
Hysterotomy and evacuation	6
Breech extraction	2
Dilatation and evacuation	1
Spontaneous abortion	1
Total	51

A total of nineteen abdominal deliveries (including thirteen cesarean sections and six hysterotomies and evacuations) were performed in this small series. Alleviation of the dyspnea, pulmonary congestion, and a lowering of the blood pressure and blood urea nitrogen levels usually followed the evacuation of the uterus. There were no maternal deaths. Because of the effectiveness of surgical procedures in preventing severe congestive failure in hypertensive patients, abdominal sections were used more frequently than in patients with rheumatic heart disease.

CONGENITAL HEART DISEASE

In this series congenital defects of the heart were diagnosed in eighteen instances. The anatomical lesions of these patients are listed in Table XII.

TABLE XII. THE TYPES OF LESIONS DIAGNOSED IN PATIENTS WITH CONGENITAL HEART DISEASE

ANATOMICAL LESION	NUMBER OF CASES
Patent ductus arteriosus	9
Interventricular septal defect	4
Coarctation of the aorta	2
Pulmonary stenosis	1
Undiagnosed	2
Total	18

Two of the eighteen patients were classified functionally in Class 3, and one in Class 4. There was one maternal death in this group in a patient with coarctation of the aorta. She died from rupture of the aorta during the eighth month of pregnancy.

Patent Ductus Arteriosus.—All nine patients did well in pregnancy and labor. One of the patients had three uneventful full-term deliveries and another had two. Digitalis was utilized prior to delivery in only one of these patients.

Interventricular Septal Defect.—There were four patients in this group. None of them developed dyspnea or cyanosis during pregnancy or labor. All were classified functionally in Class 1 or 2 throughout the entire period of pregnancy.

Coarctation of Aorta.—There were two patients with this anomaly, both of them in their first pregnancy. One had an uneventful full-term delivery aided by low forceps. The other, a 26-year-old Negro woman, developed sudden substernal oppression, dyspnea, and severe pulmonary congestion in the eighth month of pregnancy. She was immediately hospitalized, but did not respond to rapid digitalization, oxygen, and other emergency measures. She expired following severe crushing chest pain, dyspnea, shock, and collapse. The diagnosis of coarctation of aorta with left ventricular hypertrophy was confirmed at autopsy. The immediate cause of death was found to be rupture of the first portion of the aorta. Pulmonary edema, as well as congestion of the liver, kidneys, and other organs, was present.

Pulmonary Stenosis.—Only one patient with this defect was diagnosed in this series. The patient was 27 years old and para 3. Physical examination revealed a palpable thrill and harsh, blowing systolic murmur of Grade 4 intensity at the pulmonic area. There was no cyanosis or clubbing of the fingers and toes. The electrocardiogram showed a marked degree of right axis deviation and roentgenologic study showed a prominent pulmonary conus and evidence of right ventricular enlargement. It was thought that this patient had an isolated pulmonic stenosis. She developed tachycardia and shortness of breath during the eighth month of pregnancy. She was digitalized and cesarean section was performed without difficulty, under local anesthesia.

The experience with this group of patients confirms the impression that women with congenital heart disease showing no cyanosis, polycythemia, or myocardial insufficiency may carry their pregnancies and labors well. Coarctation of the aorta with very high blood pressure is an exception to this generalization.[25-30]

PAROXYSMAL AURICULAR TACHYCARDIA

In this present series of patients paroxysmal auricular (supraventricular) tachycardia was the diagnosis in six instances. All were admitted to the hospital for study and treatment. Two of these had rheumatic heart disease, and digitalis was used to control the ectopic beats in both. Digitalis therapy was used for two other patients who showed no clinical evidence of an organic heart disease. Delivery was uneventful in all of the patients.

There has been some difference of opinion in regard to the causal relationship of paroxysmal auricular tachycardia to pregnancy.[31-33] The relatively large number of such cases encountered in our series suggests that pregnancy may be one of the factors predisposing to paroxysmal tachycardia.

ACUTE BACTERIAL ENDOCARDITIS

Two patients with acute bacterial endocarditis were encountered in this series. Both were treated prior to penicillin therapy, and both succumbed. In one patient, the infection followed an incomplete abortion and, at post mortem, acute metritis and pelvic peritonitis were found with ulcerative endocarditis of the aortic and tricuspid valves. A nonhemolytic streptococcus was cultured from the blood and heart valves. In the second patient, who had badly infected teeth, the infection apparently followed delivery. Evidences of aortic valve disease and pericarditis were present clinically and a hemolytic streptococcus was cultured from the blood. Previous minimal rheumatic valvular disease had been present in this patient.

SYPHILITIC HEART DISEASE

Only one patient with cardiovascular syphilis was diagnosed. Dilatation of the ascending portion of the aorta and a moderate degree of aortic insufficiency were present. Showing no evidence of failure, the patient delivered spontaneously after an uneventful course. Cardiovascular syphilis is rarely seen in women of the childbearing age.

ARTERIOSCLEROTIC HEART DISEASE WITH CORONARY OCCLUSION

The present series includes one patient with coronary occlusion and myocardial infarction. Pregnancy occurred twenty months after the episode and the patient made an uneventful delivery. This case was reported in detail by Horwitz, La Place, Shumway, and Stroud in 1943.[34]

DISCUSSION

The physiological changes in the hemodynamics during pregnancy may make a definitive diagnosis of cardiac disease difficult. The problem of diagnosis may also be complicated by the presence of apparent cardiac enlargement, shortness of breath, edema of the lower extremities, and occasional basal râles. These symptoms and signs simulating early myocardial insufficiency may occur in the latter months of pregnancy in women with no organic heart disease.[6,16,35,36] Systolic murmurs of Grade 1 intensity are of little significance during pregnancy. This is particularly true when the murmur is heard best in the pulmonic area. However, if the patient gives a suggestive history of a previous rheumatic infection, and the murmur exceeds Grade 1 in intensity, one should consider the patient as having potential heart disease. Such murmurs can be evaluated best after delivery.

Having arrived at the diagnosis of organic heart disease, one then attempts to evaluate the functional capacity of the patient. This is most important in determining her fitness to undertake the stress and strain of pregnancy and labor.[37,38] One of the most useful procedures for gaining this knowledge is frequent examination of the heart and lungs during pregnancy and labor, seeking early evidence of heart failure. This is most often manifested by elevation of the respiratory rate, tachycardia, and the appearance of moist râles at the lung bases. In Mendelson and Pardee's[17] observation on the pulse and respiratory rates in 200 women during labor, they found pulse rates exceeding 110 and respiratory rates above 24 per minute often signified the onset of acute heart failure. Oppel,[12] in his observations, feels that a congestive condition of the lungs is the most frequent and important sign of failure during pregnancy. Because of the many factors involved, no fixed rules can be established in the management of patients with heart disease during pregnancy. We feel, as do most others, that frequent examinations throughout the period of gestation are of the greatest importance.[3,11,15,39] The two chief causes of maternal death—acute respiratory infections and cardiac failure—can be greatly reduced by careful and frequent clinical observation of the patient.

With the possible exception of patients with coarctation of the aorta, all patients functionally in Class 1 and most of those in Class 2 may be allowed to undertake pregnancy. Patients functionally in Classes 3 and 4, with or without a previous history of decompensation, and those with auricular fibrillation should be advised against undertaking pregnancy and labor. If such patients are pregnant when first examined, and have not passed the fourth month of pregnancy, therapeutic abortion is indicated. Beyond this time, conservative management is usually advisable. Close observation, adequate bedrest, strict control of diet

and sodium chloride, and judicious use of digitalis usually maintain these patients in compensation through pregnancy and labor. The earliest signs of heart failure are an indication for the administration of digitalis. Tachycardia, usually associated with increasing shortness of breath on slight effort, may be the first sign. If digitalization improves these, it can be assumed that early failure was present. Other measures are, of course, indicated, especially rest and limitation of activity. Cesarean section and hysterotomy usually are not indicated in cases of rheumatic heart disease with failure. Such procedures, however, are frequently helpful in patients with hypertensive cardiovascular disease with pre-eclampsia and eclampsia.

Since Hamilton and Thomson[2] have demonstrated that there is a normal lightening of the circulatory load during the last few weeks of pregnancy, other observers have noted the relatively rare occurrence of acute cardiac failure in the last month of gestation. They have presented convincing statistical evidence demonstrating that nonsurgical management of cardiac patients in pregnancy carries a much lower mortality rate.[2,3,6,19,40-43] Despite these observations, there are still a few who believe that abdominal delivery is justified in patients with mitral stenosis who become progressively worse despite judicious management of the heart failure.[15,44] The consensus is definitely to the contrary.

It is a common observation that heart failure may occur at any time during pregnancy, and even the most favorable cases may sometimes end tragically.[2,45] In our series, in seven of the ten patients with fatal congestive failure, failure occurred between the seventh and eighth months of pregnancy. In all, failure was due to rheumatic heart disease. They developed acute pulmonary edema with or without a preceding upper respiratory tract infection, and quickly succumbed. Bramwell and Jones[46] recently reported two similar cases and have suggested that the acute pulmonary congestion was related to sudden left auricular failure. In our series the fatalities occurred mainly in patients whose heart disease was not well controlled as the result of lack of cooperation, inadequate observation, acute infection, or the improper handling of a cardiac emergency.

In patients with acute pulmonary edema, it is imperative, if digitalization has not been previously accomplished, to give digitalis rapidly intravenously. Oxygen by positive pressure mask, intravenous aminophylline, and mercurial diuretics are additional therapeutic measures which may be life saving. If pulmonary edema develops in a patient who has been receiving digitalis, it is well to assume that the drug level is inadequate and small. Divided doses of a fast acting glycoside of digitalis (Cedilanid or Digoxin) given intravenously are indicated. Oral digitalis therapy is of no avail in such emergencies as absorption from the gastrointestinal tract is not rapid enough to be effective.

Three of our patients developed severe pulmonary edema in the first two days of the puerperium, with fatal termination. The mechanism of acute heart failure in the first twenty-four to forty-eight hours after delivery is obscure.[2,9-12,47-50] It may be that acute blood loss during delivery is an important factor which tends to increase the existing tissue anoxia and to aggravate the vascular stasis of the failing heart. The exact pathologico-physiological process, however, remains to be determined.

Acute infections, especially of the respiratory tract, may quickly convert a patient, functionally in Class 1 or 2, to Class 3 or 4, during the latter months of pregnancy. Frequent careful examinations of all pregnant patients with heart disease during the last trimester of pregnancy is imperative. Education of the patient as to the danger of infections is most important, and a system of immediate follow-up if the patient misses a regular appointment is desirable. In our series there were some patients who failed to report for their regular prenatal visits because of infectious processes. A few of these patients were later admitted to the hospital in heart failure and four died. We believe that some of these deaths might have been averted if an immediate follow-up system, as is now practiced in our clinic, had been carried out.

SUMMARY

1. A total of 26,628 pregnant women were delivered at the Pennsylvania Hospital from 1937 to 1947, inclusive. Of this total, 409 patients were found to have heart disease.

2. Of the 409 patients with heart disease, 31.3 per cent received digitalis therapy at various periods before, during, and after pregnancy.

3. There were fourteen maternal deaths, with a mortality rate of 3.4 per cent among the 409 pregnant patients with heart disease. (a) Heart failure was directly or indirectly responsible for ten of fourteen deaths. Failure occurred in seven patients between the seventh and eighth months of pregnancy and in three patients in the first forty-eight hours of the puerperium. (b) Fatal acute infections were present in seven of the fourteen patients.

4. There were fifty-four fetal deaths in this series, making a mortality rate of 13.2 per cent. Prematurity was the most common cause of fetal death.

5. Approximately 50 per cent of the patients were delivered by the use of low forceps during the second stage of labor. Abdominal delivery was used rarely for patients with rheumatic heart disease, except in the event of gynecological indications.

6. Approximately 80 per cent of the 409 patients studied were found to have rheumatic heart disease. Of these, eleven died.

7. Hypertensive cardiovascular disease was the diagnosis for fifty-one patients. These patients comprised an older average age group than the rheumatic heart disease patients. Abdominal delivery was well tolerated by this group.

8. Congenital heart disease was the diagnosis for eighteen patients. With one exception, a case of coarctation of the aorta, these patients did well.

9. Two instances of fatal acute bacterial endocarditis complicating pregnancy and delivery are reported.

10. The problem of diagnosis and management of patients with heart disease during pregnancy includes: (a) the interpretation of heart murmurs in pregnancy; (b) the prenatal care of the patient; (c) the management of acute pulmonary edema complicating pregnancy; and (d) an evaluation of the choice of anesthetic and type of delivery.

11. Careful prenatal observation, with the prevention and early control of acute respiratory infections, offers most in reducing the incidence of heart failure and the maternal mortality of this important group of patients.

We are indebted to David S. Marshall, M.D., for his valuable help in this study.

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AN APPROACH TO THE SPATIAL ELECTROCARDIOGRAM

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THE projections of the electrical forces of the heart in the frontal plane of the body can be measured from the three limb leads introduced by Einthoven.[1] It would be of interest to be able to measure these forces as they exist in three-dimensional space. The present report describes a method for this measurement which makes use of four body-surface electrode positions, first recommended by Wilson, Johnston, and Kossmann,[2] and presents studies designed to test the validity and accuracy of the method when applied to living human subjects. Data are presented on the characteristics of the mean spatial vectors in a small group of normal subjects, but no attempt is made in this report to establish the normal range of spatial vectors.

The three-dimensional characteristics of the electrical forces of the heart were first studied by Wilson in 1915.[3] While measuring potential differences between electrodes placed in various planes of the body, an electrode was placed on the precordium and another on the back to record the anteroposterior components of these forces. However, the back electrode proved to be playing little part in the writing of the deflections, for they remained the same when the back electrode was moved to an arm or leg. This was believed to be due to the nearness of the precordial electrode to the center of the electrical field, which magnified the potential variations at this electrode so that they dominated the writing of the deflection. Although such a lead could not, therefore, be used to quantitate the electrical forces, this domination of the deflection by a precordial electrode when it is paired with a remote limb electrode led to the development of precordial electrocardiographic methods used today.

In 1934 Wilson and co-workers[4] discussed certain theoretical aspects of the spatial vectors. In 1947 he, Johnston, and Kossmann[2] presented a method for calculating spatial vectors, with studies of its validity in a human cadaver. An electrode was placed at each of the three limb-lead positions, and a fourth electrode was placed on the back behind the heart, thereby forming electrically a tetrahedron which was used as a mathematical reference system on which to calculate spatial voltages. In the experiments, known voltages were impressed

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across electrodes placed in the region of the heart and then measured by this spatial method. In most instances the recorded voltages were not proportional to the impressed voltages, and the method was not considered accurate for measuring spatial forces under those circumstances.

In 1938 Arrighi[5] studied the spatial vectors in living human subjects by placing electrodes on the body to define three presumed equilateral triangles: (1) in the frontal plane, by using the three limb-lead electrode positions; (2) in a tilted horizontal plane, by using electrode positions on the two arms and a third on the back, behind the heart; and (3) in a sagittal plane, by using the back electrode with an electrode on the left side of the neck and another on the lower abdomen, a few centimeters to the left of the midline. The deflections from the leads of each triangle were treated in the manner introduced by Einthoven; and the projection of the spatial vectors on each of these planes was obtained. The method did not lend itself to the determination of the actual magnitude and direction of the spatial vectors, and the study was limited to descriptions of and inferences from the vectors as projected on each of the planes.

More recently Sulzer and Duchosal[6] have adapted vectorcardiography to spatial studies. This is a method for recording the resultant electrical axis at each instant of a given heart cycle. In their studies the electrodes were placed to define a rectangular polyhedron for the reference figure, and, from projections of the QRS "loop" on the frontal and sagittal planes, spatial "loops" were constructed.

THEORETICAL ASPECTS

To determine the size and direction of the resultant electrical forces of the heart in space the following steps must be taken: (1) the selection of electrode locations on the body surface which can be considered electrically equidistant from the heart and which define two or more known planes, and (2) the calculation of the size and direction of the mean QRS and T vectors in space from tracings taken at these electrode positions.

Regarding electrode locations, the three limb leads provide data in two of the three spatial dimensions, the vertical and the horizontal. An electrode placed on the back behind the heart may serve as a reference point from which to measure the potential differences in the third dimension. The validity of such an anteroposterior lead will depend upon the same considerations which concerned Einthoven when he presented his method for calculating the frontal projection of the electrical axis of the heart from the three limb leads. He assumed that (1) if the three limb-lead electrodes lie sufficiently far from the heart so that they may be considered electrically equidistant from it, and (2) if the tissues between the heart and these electrodes have reasonably uniform electrical conductivity, then the three limb leads can be considered to form an equilateral triangle. The deflections on the three leads can be added vectorially, using this triangle as a coordinate system, and the resultant vector will be the projection of the mean electrical force of the heart in the frontal plane of the body.

A large and controversial literature regarding the validity of these assumptions has accumulated in the thirty-five years since Einthoven's work, and an

evaluation of this literature, especially as it relates to the posterior electrode, is important in extending Einthoven's method into three dimensions.

Regarding Einthoven's assumption that the three limb electrodes are equidistant from the heart, Craib[7] immersed strips of living turtle heart in a spherical homogeneous conductor and recorded the potential differences between two electrodes as they were moved to a series of positions of known and regularly increasing distance from the muscle strip. He found that the amplitude of the deflection varied inversely with the square of the distance between the electrodes and the heart. Thus, the distribution of the electrical field surrounding heart muscle in such a medium resembled the distribution of the electrical field of a single dipole in a volume conductor. This distribution is such that when the amplitude of the deflection is plotted against the distance of the electrode from the dipole, an extinction curve is formed. Thus, electrodes more than a certain distance from the dipole are relatively equidistant from it in an electrical sense, even though they are not equidistant from it anatomically. These studies supported Einthoven's assumption, for, if the three limb electrodes were placed outside the immediate region of the heart, they might be electrically equidistant from it, provided the body were as homogeneous in conducting properties as Craib's sphere.

Wilson,[3] and later Arrighi[5], studied this amplitude-distance relationship in the living human subject by plotting a series of points from the precordium to the pubes, and then measuring the potential differences between electrodes moved to these successive points. The amplitude of the deflections diminished rapidly as the electrodes were moved from the general vicinity of the precordium, but beyond about 12 cm. from the heart, further changes in amplitude were negligible. Thus, the distribution of the electrical forces of the heart in man appeared to have an inverse square relationship with distance, as if the heart were a single central dipole; and, since Einthoven's limb-lead electrodes were more than 12 cm. from the heart, they could, then, be considered to be relatively equidistant from it electrically. Helm and associates[8] obtained the same results in a similar type of study. However, when they studied a series of electrode positions extending from the precordium to the shoulders in the same way, the diminution in amplitude at successive electrode positions was less clear. From this and other studies, they concluded that the body may not be sufficiently homogeneous in conductivity to justify Einthoven's hypothesis. However, because the chest is convex in contour from the precordium to the shoulders when the subject is supine, the successive electrode positions studied represented not only changes in distance from the heart, but also changes in angle of projection, the effect of which could not be evaluated in their experiments.

As for the anatomical distance from the heart to the back electrode, Arrighi[5] measured this distance in many of his subjects by x-ray examination, and found that in all instances it exceeded 12 centimeters. Similar measurements were made in many of the subjects of the present report, with like results. These distances were compared with the distance from the heart to the left shoulder in the same subjects, as seen in frontal teleroentgenograms, and it was found that the heart-to-back radius was as large as and occasionally larger than the radius

to the left shoulder. Since the arms do not participate in the distribution of the electrical field of the heart, the left arm electrode lies, in effect, at the left shoulder; therefore, both the back and left arm electrodes can be considered to be about 12 centimeters from the heart in most subjects. If the body is a satisfactorily homogeneous conductor, these, and the left leg and right arm electrodes, are then roughly equidistant from the heart electrically.

Regarding Einthoven's second assumption, that the body is an adequately homogeneous volume conductor, there have been no direct studies of electrical conductivity in the living human subject. Eyster and co-workers,[9] studying the electrical field of the living turtle heart, found that upon gradual movement of two electrodes out from the center of the electrical field, the diminution in amplitude of the deflection took place somewhat more slowly when the heart was in situ and surrounded by tissue than when it was placed in a saline-containing conductor. The nonsphericity of the turtle body also appeared to play a part in the delayed slope of the amplitude-distance curve, for when the heart was in its shallow plastron but surrounded by saline, the fall in amplitude was slower than when the heart was in a saline-containing sphere. In the cadaver experiments of Wilson and associates[2] the posterior component of the impressed voltage was always greater than that calculated from the tracings. This suggested that the tissue resistance was less in the anteroposterior plane than in the frontal plane. As the authors stated, the effects of tissue death (the cadaver was one week old) make these data difficult to interpret for the living body, for death rapidly alters the specific resistance of tissue.[10]

In studies of isolated living tissues of the dog, Eyster and co-workers[9] found blood to be the best conductor, and muscle, being well supplied with blood, a better conductor than visceral tissues. Johnston and Kaufman[10] examined the specific resistance of various living tissues in the dog, and concluded that although the differences from tissue to tissue were definite, they were of a relatively small order, and the distortion of the electrical field of the heart due to these differences was probably negligible.

In summary, it is likely that, electrically, the back electrode is as adequately remote from the center of the electrical field of the heart as are the limb electrodes, and although the body does not have perfectly uniform conductivity, the distortion of the electrical field due to this may be slight.

Having selected electrode positions which are electrically satisfactory, a mathematical system of coordinates must be devised upon which the spatial vectors can be calculated from tracings taken between these electrode positions. The mathematical system will depend, of course, upon what geometric figure these electrode positions are believed to define electrically on the body. They may be considered to lie on the surface of a cylinder, at the apices of a rectangular polyhedron, or at the apices of a tetrahedron, etc. Actually it will not matter which geometric reference system is used, provided it resembles the electrical relationship of the heart to the electrode positions and to the planes in the body they define. The tetrahedron was selected because of its geometric simplicity and because it is closely allied as a geometric figure to the Einthoven triangle. This figure, which was first suggested for spatial vector calculation by Wilson

and associates[2] is a four-sided pyramid with the three limb leads defining its base and the back electrode its apex. Since, anatomically, the center of the heart lies within or possibly even slightly anterior to the frontal plane of the body as defined by the three limb-lead electrodes, a tetrahedron with its origin at the midpoint of its base and its four apices equidistant from this point would appear to be the most appropriate figure; this figure is the isosceles tetrahedron. Other regular tetrahedrons were studied, with origins at varying distances posterior to the frontal plane. Under the circumstances of these experiments, none of the alternative figures proved to be more valid than the isosceles tetrahedron, and, therefore, this figure was used in the following experiments.

METHOD

Twenty normal young men were studied. Electrodes were placed on the three limbs as in taking conventional limb leads, and a fourth electrode was placed on the back directly behind the heart. This point was usually 3.0 to 4.0 cm. inferior to the left scapula and about 3.0 cm. to the left of the midline. The subjects were in the semireclining position and were not moved during the recording period. After Lead III was taken, a bipolar Back-to-Left-Leg Lead was recorded. In this lead the negative electrode was connected to the back, and the positive electrode to the left leg.

The mean magnitudes of the deflections on each lead were calculated by measuring the area of the complexes. For the QRS complex this was done by adding algebraically the products of one-half the width times the height of every component of the complex; for the T wave, the enclosed squares were counted. The P-R segment was used as the baseline for both the QRS complex and T wave. Five to six complexes were measured from each tracing, and the results were averaged. The values for the QRS complexes and T waves on the standard limb leads were plotted on the triaxial reference system and vectorially added, giving the magnitudes and directions of the frontal projections of the mean spatial vectors. To determine their magnitudes and directions on the sagittal plane, the projections of the frontal plane vectors on the 90° frontal median of the triaxial system were measured, and these magnitudes were added vectorially to the magnitudes measured from the Back-to-Left-Leg Lead on a biaxial coordinate system, a 45° angle between the two axes (Fig. 1). For mathematical accuracy in the isosceles tetrahedron, the observed magnitudes of the QRS complex and the T wave on the Back-to-Left-Leg Lead must be increased by $\sqrt{1.5}$; however, this was not usually done because the correction was so small. The projections of the ventricular gradient on the frontal and sagittal planes were determined by vectorially adding the mean QRS and T vectors on each plane. Models of the tetrahedron reference figure were made from small wooden applicators, and the mean spatial vectors were mounted to scale in size and direction. These models were of considerable help in visualizing the projection of the spatial vectors on various planes of the body.

To calculate the mean spatial vectors from their projections on the frontal and sagittal planes, a Cartesian coordinate system was selected consisting of three mutually perpendicular axes: (1) a vertical axis which is a median at

90° in the frontal plane, (2) an anteroposterior axis which extends from the origin to the apex of the tetrahedron in the sagittal plane, and (3) a horizontal axis which is Lead I of the frontal plane. The components of the vectors on these axes were determined by dropping perpendiculars from the axes to the ends of the vectors on the appropriate plane. The magnitude of the mean vectors in space were calculated from the equation:

$$Magnitude\ of\ Vector\ V = \sqrt{a^2 + b^2 + c^2},$$

where a is the component on the vertical axis, b the component on the anteroposterior axis, and c the component on the horizontal axis. The components for the QRS, T, and ventricular gradients were each, in turn, substituted in the

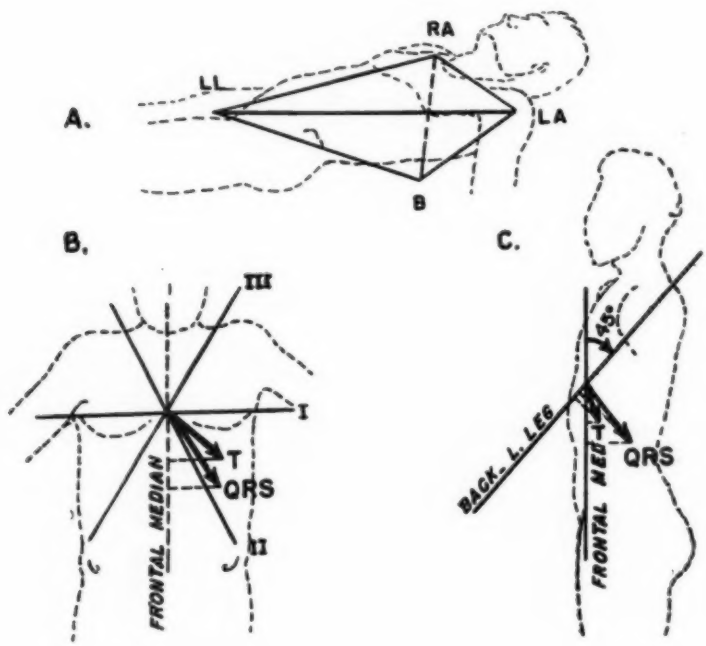

Fig. 1.—*A*, the isosceles tetrahedron defined by four electrode positions. The base is in the frontal plane of the body and is an equilateral triangle. The four apices are equidistant from the mid-point of the base. *B*, the triaxial reference system for calculating the mean vectors in the frontal plane from the three limb leads. *C*, the axis system for calculating the mean vectors in the sagittal plane.

equation, giving the mean spatial QRS, T, and ventricular gradient. In Bayley's nomenclature[14] these are the SA_{QRS}, SA_T, and SA_G. The angles between the mean spatial vectors were calculated from these same components by appropriately substituting in the equation:

$$\cos\ \theta = \frac{(QRS_a \times T_a) + (QRS_b \times T_b) + (QRS_c \times T_c)}{SA_{QRS} \times SA_T}$$

where θ is the angle between the mean spatial QRS and T vectors.

STUDIES OF THE VALIDITY OF THE METHOD

I. If this method for calculating the spatial vectors is accurate and the assumptions upon which it is based are correct, the projections of the mean electrical forces of the heart on any known plane in the body should have magnitudes and directions which are predictable from the calculated mean spatial vectors. This possibility was first tested by selecting a plane through the right upper abdomen. An electrode was placed 3 cm. below the right costal margin

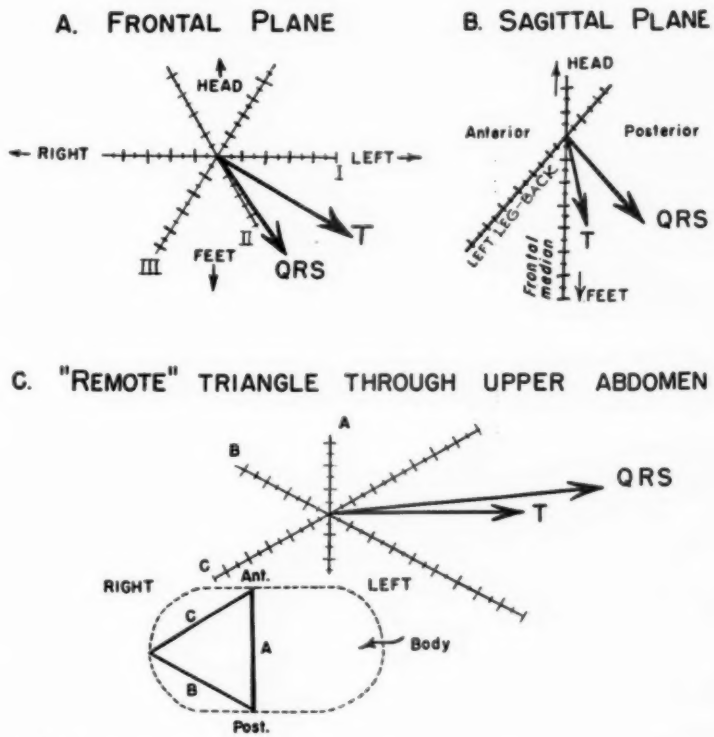

Fig. 2.—*A* and *B*, the frontal and sagittal projections from which the mean spatial vectors were calculated. *C*, the mean QRS and T projected on a plane through the right upper abdomen. The electrodes defining this plane were placed so as to form Leads A, B, and C. See text for discussion.

in the midclavicular line, another on the lateral margin of the right quadratus lumborum muscle, and a third in the right mid-axillary line, forming a horizontal plane through the right side of the abdomen. Since the electrode positions were selected to be satisfactorily remote from the heart and to define an equilateral triangle, the magnitudes for the QRS and T on the three experimental leads were vectorially added on a triaxial reference system. The resultant vectors were, then, the projections of the cardiac vectors upon this remote horizontal plane. A model of these vectors was constructed and visually superimposed on the model of the spatial vectors (the two held to resemble the anatomical relationship that the three electrodes had with the heart). Such an experiment is illustrated in Fig. 2.

It was found that when the anterior edge of the experimental triangle was tilted inferiorly about 15°, the vectors of the two models superimposed closely. To confirm this, a mathematical method was devised for calculating the size and direction of projections of a spatial vector upon a remote plane of known inclination. There was reasonable agreement between the two methods in each of the experiments.

The projections of the cardiac vectors upon a series of sagittal planes through the body were studied by this same geometric method. These planes were defined by three electrode positions, one on the left leg, and the other two on the ends of anteroposterior axes through the shoulders, through the midclavicular areas, and through the sternoclavicular areas bilaterally. In Fig. 3 are shown the projections in one subject of the cardiac vectors on two of these diverging sagittal planes, as well as the projections on the sagittal plane of the tetrahedron. The mean vectors proved to be largest on the plane through the right shoulder, intermediate on the sagittal plane, and smallest on the plane through the left shoulder. This difference in magnitude of the projections is readily explained by the slightly leftward direction of the mean spatial vectors in the frontal plane; the plane through the right shoulder is nearly parallel to the spatial vectors, whereas the sagittal plane, and, to a greater extent, the plane through the left shoulder are oblique to the spatial vectors and therefore have correspondingly smaller components projected on them. The angles between the QRS and T vectors on the experimental planes are smaller than the angle on the true sagittal plane because the former planes are defined by isosceles and not equilateral triangles. Nevertheless, the size and direction of the projections of the cardiac vectors upon these planes tend to resemble projections of the calculated spatial vectors on such planes.

Since the frontal plane defined by the three limb leads lies considerably behind the anterior surface of the body, another remote plane to compare with the spatial vectors could be constructed which would be tilted anteriorly to the frontal plane of the tetrahedron. Two electrodes were placed on the most anterior surfaces of the chest, each as near a shoulder as possible, while the third electrode remained on the left leg. The projections of the electrical forces of the heart on this plane were calculated from tracings taken between these electrodes as in the previous experiments, and a model of the resultant vectors constructed. Fig. 4 illustrates such an experiment. When the experimental plane model was tilted at its superior edge about 20° anteriorly to the frontal plane of the spatial vector model, the vectors of the two systems were closely superimposed.

Summary: In these experiments, the projections of the mean QRS and T vectors on a variety of planes, frontal, horizontal, and sagittal, were compared with the projections which the tetrahedral mean spatial vectors would produce on these same planes. In all instances there was reasonable agreement between the two methods.

II. Since this method for spatial vector construction depended upon the assumption that the four electrodes were electrically equidistant from the heart, studies were undertaken to determine how adequately remote these electrode

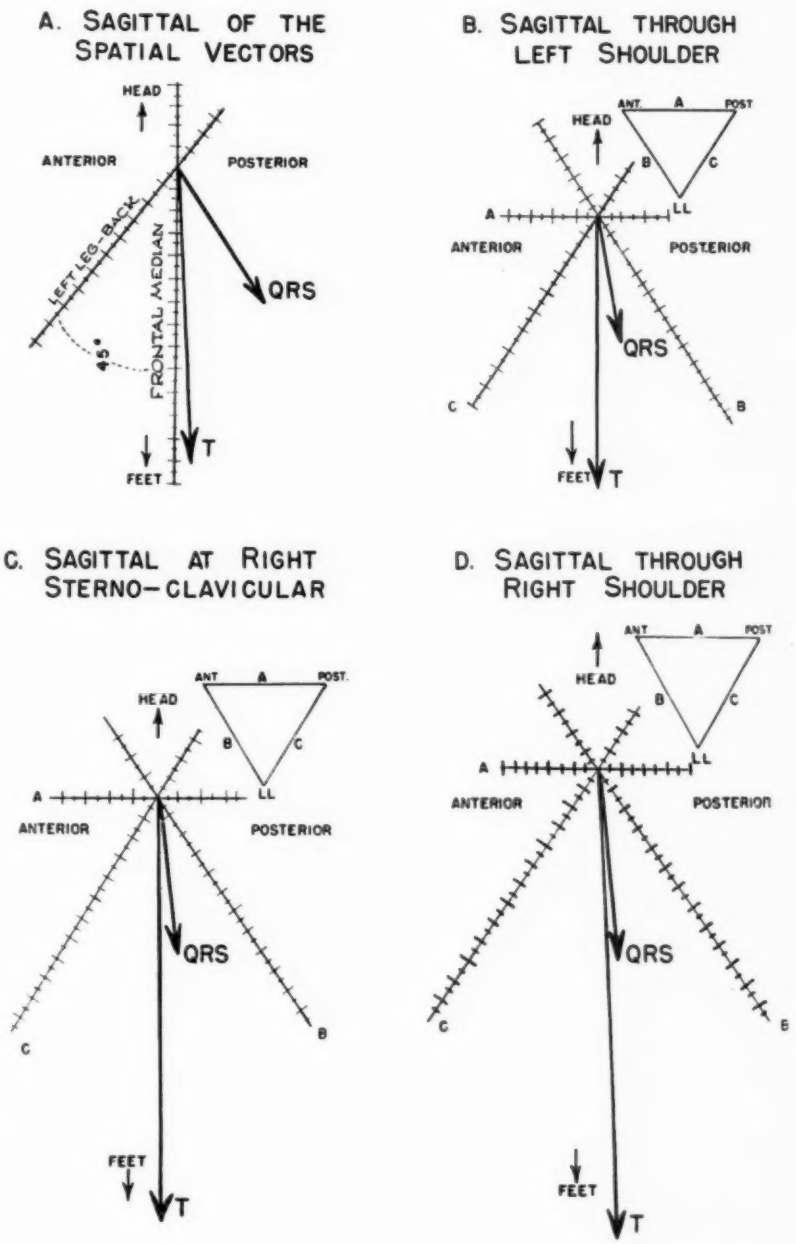

Fig. 3.—*A*, projections of the mean spatial vectors on the sagittal plane of the body as defined by the tetrahedron. *B*, *C*, and *D*, projections of the mean spatial vectors on three diverging sagittal planes in the same subject. The left leg electrode remained in place and the two other electrodes were placed on anteroposterior axes through the right and left shoulder and the right sterno-clavicular region, to form Lead A for each triangle. See text for discussion.

positions were. It is not possible to move the back electrode nearer the center of the field. However, the left arm electrode can be moved to positions nearer the heart. Furthermore, as was discussed earlier, the left arm electrode is anatomically about as far from the heart as the back electrode, and, therefore, the validity of one may shed light on the validity of the other. First, the left arm electrode was placed at a number of different positions on and around the left shoulder, and the spatial vectors were determined for each position. The resultant vectors differed by no more than 7 per cent which is within the range of error in

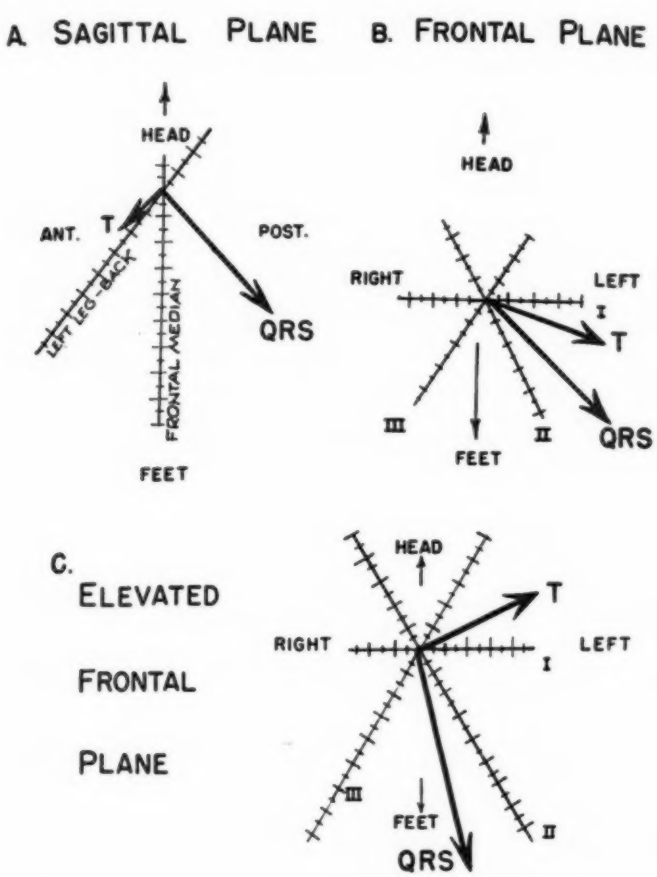

Fig. 4.—*A* and *B*, the frontal and sagittal projections from which the mean spatial vectors were calculated. *C*, the projection of the vectors on a plane through the body which lies anteriorly to the frontal plane of the three limb leads at its superior edge. See text for discussion.

the method. Then, the electrode was moved to a series of positions on the left anterior chest and precordium. Using the same tetrahedral reference figure for each of these positions, the spatial vectors were calculated. As the electrodes were moved from point to point toward the precordium, the spatial vectors

began to change. At first slightly, then more markedly, they became larger and drifted in direction toward the left shoulder.

In several subjects, however, the mean spatial T vector showed this distortion before the QRS vector. This difference between the electrical fields of the QRS and T could not be due to a fundamental difference in their manner of propagation through the body for, although the T wave may represent a longer lasting dipole and less dense field per unit of time than the QRS, this would not produce a different type or distribution of electrical field. Nor is it likely that the systolic contraction of the heart would shift the anatomical region of greatest electrical intensity enough to be detectable in body surface derivations. A more satisfactory explanation points to the difference in direction of the two spatial vectors, for when a remote electrode is moved toward a dipole along a line perpendicular to the dipole, it crosses fewer isopotential lines, and, therefore, the deflections it records show less change in amplitude than when the electrode is moved the same distance along a line parallel to the dipole. In all the subjects of this study, the mean spatial QRS was more posteriorly directed than the T, and in the subjects under discussion, the angle between the QRS and T measured from 30° to 45°. Therefore, the mean spatial QRS vector may have shown less change than the T vector at these successive electrode positions because it was more perpendicular to the plane along which the electrode was being moved.

Summary: From these studies of the effect on the spatial vectors of changing the position of the left arm electrode, it is evident that electrode positions on and around the left shoulder are, electrically, adequately remote for spatial studies. Only when the electrode was well advanced onto the anterior chest did the distortions of the spatial vectors become really significant. The fact that the QRS and T vectors did not change simultaneously and proportionately indicates that even at these distorting positions which were no longer "adequately remote," the electrode was qualitatively recording the QRS and T waves as if they were produced by single QRS and T vectors.

III. When the position of the heart in the chest is altered, as in full inspiration, the mean spatial vectors should shift in position but not in magnitude, if this method for calculating the vectors is valid. Furthermore, it has been shown in dogs that the specific resistance of the lung is increased as much as 1,000 ohm-cm. upon inflation.[10] Therefore, the study of the effect of inspiration on the mean spatial vectors in the human subject might clarify the role of the electrical resistance of the lungs in the distribution of the electrical field in man. Some workers have felt that the resistance of the air-filled lung may be so much greater than that of the other tissues surrounding the heart, that Einthoven's hypothesis that the body is a relatively homogeneous conductor of the electrical field of the heart is not valid.[8,11] In twelve normal subjects, the spatial vectors were calculated at rest and on full inspiration. In all instances the mean spatial QRS vectors shifted in direction, becoming more vertical and more parallel with the frontal plane; in no instance did the QRS change more than 10 per cent in magnitude though it underwent a rotation of up to 30°. These results indicate

that an increase of the specific resistance of the lung on inspiration has little effect on the magnitude of the electrical field of the heart.

On the other hand, the mean spatial T vector became shorter by more than 20 per cent in ten of the twelve subjects; in six subjects the T vectors rotated away from the direction of rotation of the QRS, and in two instances a definitely abnormal spatial ventricular gradient was produced. These changes in the mean spatial T vector were not believed to be due to an increase in the electrical resistance of the inflated lungs, for similar changes were not seen in the QRS vector. Furthermore, in some instances this alteration appeared to be gradual, its completion requiring several complexes after full inspiration had been reached. A shift in the direction of the T waves on inspiration has been used by Goldberger[12] to study the rotation of the electrical field during respiration, with the assumption that the act of inspiration had no effect on the nature or distribution of the electrical forces; others[13] have suggested that changes in the direction of the T wave on inspiration discordant from those for the QRS complex are evidence of myocardial abnormality. From the studies presented here, it is likely that the changes in the T vector on inspiration involve actual change in the electrical characteristics of the vector, and may occur in apparently normal individuals. The cause of this change in the T vector will be the subject of a subsequent report.

ANALYSIS OF THE MEAN SPATIAL VECTORS IN TWENTY NORMAL SUBJECTS

Since, from these experiments, it is probable that the tetrahedral method for calculating mean spatial vectors is valid and the readings are correct, a survey of the findings in a small number of normal subjects is justified. It was not the primary purpose of this study to collect data on a large group of subjects, but rather to explore the validity and implications of the method. Therefore, conclusions regarding the characteristics of the mean spatial vectors in the normal subject cannot be comprehensive. These 20 subjects were healthy men between the ages of 20 and 30 years.

In the majority of subjects the mean spatial QRS and T both pointed within a range of 20° anteriorly and 45° posteriorly (in relationship to the frontal plane). In all instances the T vector was directed leftward and anteriorly to the QRS vector. The average T pointed 3° anteriorly to the frontal plane, and the average QRS pointed 20° posteriorly. The magnitudes of the vectors varied more than did their directions: the mean spatial QRS vector from 20 to 60 microvolt-seconds, the T from 20 to 80 microvolt-seconds, and the gradient from 40 to 120 microvolt-seconds. All of these are within the normal range by Ashman's analysis.[14] In most instances the T vector was larger than the QRS. Occasionally the reverse was true, or both would be strikingly smaller or greater than the average. Because the range in magnitude was so wide, it was impossible to anticipate the degree of anterior or posterior deviation of a vector by its size projected on the frontal plane; that is, a vector with a conspicuously short projection on the frontal plane did not necessarily have a large posterior component. The angle between the mean spatial QRS and T vectors was found to be within

a range somewhat greater than has been anticipated in the literature,[14] from 11° to 49°, and the majority under 20°. The angle between the spatial T and the spatial gradient varied from 5° to 27°, with five of the twenty patients over 20°, all within the normal range defined by Ashman.[14] In this study no attempt was made to calculate the ventricular gradient-anatomical axis angles.

DISCUSSION

Under the circumstances of these experiments the tetrahedral method for calculating the mean spatial vectors of the heart appears valid. The discrepancies (rarely exceeding 15 per cent) encountered between predicted and actual vectors on the various experimental planes of the body are easily attributable to technical errors in the method, such as the impossibility of perfect electrode placement in defining the experimental planes and the inaccuracies involved in calculating the mean areas of the deflection. Furthermore, the particular isosceles tetrahedron used almost certainly is an oversimplified representation of the electrical field of the heart, and hence, another source of error. It is likely that, electrically, every individual represents a different tetrahedron. In spite of such schematized and simplified treatment of the electrical field, the method proved to be valid in all subjects studied.

These results affirm Einthoven's assumptions that the three limb lead electrodes (and the back electrode) are electrically relatively equidistant from the heart, and that the body has satisfactorily uniform conductivity. This conclusion is not meant to deny that various tissues and even large areas of the body differ in their electrical properties. Such variations evidently are of too small an order to be detected even by such relatively precise methods as those described in this study, and in electrocardiographic studies based on body surface derivations, these variations can apparently be ignored. Modern electrocardiographic methods must be recognized, then, as giving only extremly general notions of the electrical characteristics of the heart and interposed tissues. Determining the cardiac vectors is, in effect, a method of generalizing the electrical field of the heart from the total deflection in several leads. Therefore, to base the clinical interpretation of the electrocardiogram on such an analysis of the mean QRS and T vectors would not only be a rational approach to electrocardiography, but would also appear to be a more accurate and reliable method than one based on memorizing contours and sizes of deflections on the various leads.

CONCLUSIONS

1. A method for determining the mean size and direction of the electrical forces of the heart in three-dimensional space is described. Four electrode positions are used, the three limb lead electrode positions and one on the back, directly behind the heart. These four electrode positions form, electrically, an isosceles tetrahedron, which is the mathematical reference figure used in this study.

2. The method was found to be reasonably accurate in a series of experiments on living human subjects. The results of these studies affirm the principal

assumptions upon which the Einthoven triangle and the present concept of cardiac vectors is based; that is, the electrodes are relatively equidistant electrically from the heart, and the body is an adequately homogeneous conductor of electricity.

3. The characteristics of the mean spatial QRS, T, and ventricular gradient in a small group of normal young males are presented.

The author wishes to express his gratitude to George E. Burch, M.D., in whose laboratory and under whose supervision these studies were conducted, and James Cronvich, M.S., School of Electrical Engineering, Tulane University, for his assistance in solving the mathematical and physical problems which this work posed.

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CHOLESTEROL CONTENT OF THE CORONARY ARTERIES AND BLOOD IN ACUTE CORONARY ARTERY THROMBOSIS

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DISTURBANCES in lipoid metabolism are being demonstrated with greater frequency as important factors in the pathogenesis of coronary artery sclerosis and thrombosis.[1-6] It has been shown repeatedly that abnormal increases in the blood cholesterol are associated with increased deposition of cholesterol in the aorta and the coronary arteries.[7-11] Previous studies have demonstrated that the concentration of cholesterol in the aorta is directly related to the amount of atherosclerosis present.[6,12] This was found to be true as well for the renal arteries.[13]

No data appears to be available from the literature on the quantitative cholesterol content of the coronary arteries in normal individuals or in patients with coronary arteriosclerosis such as those who died of coronary thrombosis, although previous studies have reported biochemical analyses of the cholesterol content of the aorta and of the renal arteries.[6,12,14,15] We believed such information would be of interest and therefore studied (a) the cholesterol content of the anterior descending branch of the left coronary artery in a group of eleven patients who had died of acute coronary artery thrombosis and in a comparable group of fourteen patients who died of causes other than coronary artery thrombosis, (b) the blood serum cholesterol and ester levels in both of these groups, and (c) the gross appearance of the aorta and coronary arteries for evidence of atherosclerosis in these patients. From the coronary ostium the first 6 cm. of the left anterior descending branch of the coronary artery, including the adventitia, was dissected out in each. All perivascular areolar (including the fatty) tissue was carefully dissected off the coronary artery.

It has been shown by various investigators that the total cholesterol, cholesterol ester, free cholesterol, and other lipid content of the atheromatous arteries are similar in composition and ratio to these same lipids in the blood.[5,6,19,20] Certain of these authorities interpreted these findings as indicative of the hematogenous origin of the lipoidal material deposited in the arteries.[4,20]

METHODS

The method of cholesterol determination of the coronary artery was that described by Faber[14] and Bjornsson.[16]

The determinations of blood cholesterol and cholesterol ester were made by the Sperry-Schoenheimer method[17] as modified by Chaney[18,21] and Lovell.[18]

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PATIENT MATERIAL

A total of twenty-five patients was studied post mortem as described in Tables I–III. A larger group of patients was undertaken but owing to accidents in the course of the study a number had to be discarded.

TABLE I. ELEVEN CASES OF ACUTE CORONARY ARTERY OCCLUSION

CASE NUMBER	SEX	AGE	MILLIGRAMS CHOLESTEROL PER GRAM OF CORONARY ARTERY	BLOOD CHOLESTEROL (MG.)	GROSS GRADE OF CORONARY ARTERIOSCLEROSIS
1	M	51	25.8	385	4
2	F	66	35.0	348	3
3	M	74	10.8	215	2
4	M	70	36.5	282	4
5	M	55	11.4	354	4
6	M	38	28.4	411	4
7	F	72	24.8	281	4
8	F	67	8.9	304	4
9	M	72	9.4	210	4
10	F	72	23.0	287	3
11	M	68	10.8	280	3
Averages		64	20.4	303	3.5

Table I describes the findings in a group of eleven patients who died of an acute coronary artery thrombosis. It is seen that the average age for this group is 64 years as compared to 62 years in the "control" group. The range in ages was 38 to 74; four patients were women and seven were men. The average cholesterol content of the coronary artery was 20.4 mg. per gram of dried coronary artery weight with a range of 8.1 to 36.5 milligrams. The average blood cholesterol was 303 mg., an abnormal reading with a range of 210 to 411 milligrams. The average gross grade of coronary arteriosclerosis was 3.5.

The cholesterol content of both the blood and the coronary arteries was analyzed in fourteen patients who had died of causes other than coronary artery occlusion, as shown in Table II. The average age of this group was 62 years; nine patients were women, five were men; the ages ranged from 45 to 87 years. The average milligram content of cholesterol per gram of dried coronary artery weight was 5.1 with a range of 0.6 to 8.1 milligrams. The average blood cholesterol was 186 milligrams, ranging from 148 milligrams to 241 milligrams; the normal figures are from 140 milligrams to 220 milligrams. The cholesterol ester and free cholesterol components were determined but are not described since there was no apparent difference between the cholesterol ester and the free cholesterol in the two groups of patients.

The degree of arteriosclerosis of the coronary arteries was described according to the grade of involvement as follows: N indicates normal or no palpable or grossly visible coronary arteriosclerosis; Grade 1 indicates a slightly palpable or grossly visible coronary arteriosclerosis; Grade 2 indicates a moderate degree of coronary arteriosclerosis; Grade 3 denotes a marked degree of coronary arteriosclerosis; Grade 4 designates the most extensive involvement of the coronary arteries by arteriosclerosis.

It is noted that in the group of patients who did not die from coronary artery occlusion the average grade of coronary arteriosclerosis was 1.5 (Table II).

TABLE II. FOURTEEN CASES OF DEATHS DUE TO CAUSES OTHER THAN CORONARY ARTERY OCCLUSION (CONTROLS)

CASE NO.	SEX	AGE	MILLIGRAMS CHOLESTEROL PER GRAM OF CORONARY ARTERY	BLOOD CHOLESTEROL (MG.)	GROSS GRADE OF CORONARY ARTERIOSCLEROSIS	CAUSE OF DEATH
1	F	55	6.7	148	N-1	Carcinoma of uterus
2	F	68	6.8	178	2	Carcinoma of colon
3	F	45	0.6	155	N	Acute ulcerative colitis
4	M	66	4.5	182	2	Carcinoma of larynx
5	F	87	5.5	152	3	Carcinoma of colon
6	F	62	6.0	165	2	Cirrhosis of liver
7	F	51	6.4	241	1	Carcinoma of ureter
8	F	84	8.1	205	3	Pneumonia
9	M	53	1.0	174	N	Cirrhosis of liver
10	M	62	1.0	201	N	Carcinoma of esophagus
11	M	60	5.2	215	2	Carcinoma of bronchus
12	F	71	6.5	191	2	Hypertension, cerebral hemorrhage
13	F	55	7.0	165	2	Carcinoma of peritoneum
14	M	48	6.6	236	1	Hypertension, cerebral hemorrhage
Averages		62	5.1	186	1.5	

COMMENT

Table III reveals a comparative analysis between the two groups of patients. It is seen that the average cholesterol content of the coronary arteries of the patients who died of an acute coronary artery thrombosis is four times as great (20.4 mg.) as the average cholesterol content of the control group (5.1 mg.) of patients who did not die of coronary artery thrombosis. In addition, Table III compares the average blood cholesterol levels in both groups of patients and reveals a considerably higher level in the coronary occlusion group (303 mg.) as compared to the control group (186 mg.).

TABLE III. COMPARISON OF CHOLESTEROL CONTENT IN CORONARY ARTERY AND BLOOD—TWENTY-FIVE CASES

CAUSE OF DEATH	AVERAGE AGE	MILLIGRAMS CHOLESTEROL PER GRAM OF CORONARY ARTERY (AVERAGE)	AVERAGE BLOOD CHOLESTEROL (MG.)	AVERAGE GRADE OF CORONARY ARTERIOSCLEROSIS
Acute coronary thrombosis	64	20.4	303	3.5
Noncoronary deaths	62	5.1	186	1.5

It is of interest to note that in the control group (Table II) the 5.1 mg. cholesterol content of the coronary artery is practically the same (1.9 per cent difference) as the value given by Bruger and Chassin[13] for the renal artery in their control patients. Theirs was a study of the cholesterol content of the renal arteries in the nephrosclerosis of patients who died of hypertension.

The post-mortem findings of hypercholesterolemia in the group of patients who died of acute coronary artery occlusion is in keeping with the hypercholesterolemia found by Morrison, Hall, and Chaney[21] in a series of patients who had survived an acute coronary thrombosis.

SUMMARY

1. The average cholesterol content of the coronary arteries in a group of patients who died from an acute coronary artery thrombosis was four times as great as the average cholesterol content of the coronary arteries in a comparable group of control patients.

2. Hypercholesterolemia was found in most of the patients who died of acute coronary artery thrombosis, as compared to a normal blood cholesterol average in the comparable control group.

3. These findings suggest that a disturbance in lipid metabolism is a factor in the pathogenesis of atherosclerosis.

We wish to express our appreciation to Albert L. Chaney, Ph.D., Charles Langmade, M.D., and Miss Perla Berlin, B.S., for their aid in this investigation.

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FACTORS INFLUENCING THE T WAVE OF THE ELECTROCARDIOGRAM. AN EXPERIMENTAL STUDY EMPLOYING INTRACAVITARY AND EXTRAVENTRICULAR (EPICARDIAL) LEADS

I. Effects of Heating and Cooling the Endocardium and the Epicardium

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ONLY recently has the question been raised as to the contribution of depolarization and repolarization of the subendocardial lamina to the genesis of the electrocardiogram.[1-12] The employment of intracardiac catheter electrodes has facilitated the study of the electrical influence of the myocardium. The electrical effect of laminar injury of subendocardial myocardium recently was clarified by the use of this newer technique.[10] Briefly, it was demonstrated that injury of the subendocardial myocardium produced definite injury effects, recorded on intracavitary and epicardial leads. The direction of the RST-T displacement in either subepicardial or subendocardial injury depended purely upon the spatial orientation of the exploring electrode in relation to the theoretical surface between injured and uninjured areas.

In the present study, a similar technique was employed to investigate the genesis of electrical events established by changes in the rate and direction of repolarization of subepicardial and subendocardial lamina. These changes were produced by cooling and heating the epicardium and endocardium. Particular information was sought to clarify the contribution of the electrical effects of retarded and accelerated subendocardial muscular laminar repolarization. Some investigators have held that this part of the myocardium contributes little.[4,6,11] Recently, however, experimental evidence has been presented that changes in the electrical state of the subendocardial muscle play a part in the genesis of the electrocardiogram.[10,12] Hitherto, changes in the direction of the T wave produced by thermal changes have been interpreted as being due to summation effects of dextro- and levocardiograms,[13-15] or on the basis of the relative speed of repolarization of apical and basal parts of the heart.[6,16-20] Although direct epicardial leads and indirect leads have been used in the study of the effects of heating and cooling the heart, in dog, man, tortoise, turtle, and calf, since the days of Burdon-Sanderson and Page in 1880,[16] exploratory intracavitary leads have not previously been used in such experiments.

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Our method of changing the temperature of the subendocardial surface relative to that of the epicardium consisted of introducing physiological saline at various temperatures, through intracavitary catheter electrodes. The epicardial and intracavitary electrocardiograms were recorded before, during, and after the temperature change was produced. Byer[3] induced temperature changes in a similar manner but produced cardiac standstill before producing the temperature change. This procedure itself produces significant T-wave changes.

Clinically, large, upright T waves with prolonged electrical systole have been observed in patients with hypertensive encephalopathy.[2] These changes have been ascribed to ischemia involving preponderantly subendocardial muscle of the left ventricle. A similar explanation may be invoked where high T waves occur in precordial leads preceding the usual RS-T changes and negative T-wave stages of myocardial infarction.[21-24,28] On the basis of the results of the following experiments, we believe that the conclusions just stated were correct. Although the fundamental postulates of modern electrocardiographic theory can be used to anticipate the form of the intracavitary electrocardiogram in clinical subendocardial ischemia, and in animal experiments with localized retarded and accelerated repolarization, direct evidence has not previously been presented. Byer and associates[3] speculated on the direction of the T wave in the ventricular cavity in similar experiments, but failed to produce direct experimental proof thereof.

METHODS

Ten dogs weighing 8 to 16 kilograms were anesthetized with intravenous pentobarbital sodium (25 mg. per kilogram). The exploring intracavitary electrode used was a modified form of one previously described.[10] It consisted of a ureteral catheter or an insulated metal tube, through which a small enamel-coated copper wire was threaded. A small pellet was soldered to the end of this wire, which protruded approximately 2.0 mm. beyond the tip of the catheter. Two holes, each 1.0 mm. in diameter, were made on the sides of the distal 1.0 cm. of the catheter. On the other end a Luer-Lok arrangement made possible the injection of solutions through the catheter. Thus, the tip of the electrode recorded changes induced locally by the injection of saline of various temperatures. The intracavitary electrode was introduced into the right ventricle via the external jugular vein, usually the right, and into the left ventricle through the common carotid, also usually the right. With experience, the electrode could be easily inserted, and its exact location while it was being passed could be correctly anticipated by the changes in the P and QRS complexes as the tip passed the region of the S-A node and the A-V ring, and by the marked increase in potential when the cavity was entered. The electrode was gently pushed until the apex of the ventricle was reached, to produce slight RS-T elevation. Then the electrode was withdrawn 1.0 cm., and the RS-T segment returned to the isoelectric line. The upper end of the electrode was securely fixed in the neck by stay sutures. It was found that the position of the electrode remained constant for hours, without injury effects. In every instance, careful necropsy examination was used to confirm the position of the electrode, and to determine whether the tip of the electrode had produced any damage. In the majority of experiments semi-

unipolar leads were satisfactorily used, with the exploring electrode in the subcutaneous tissues superjacent to the anterior apical portion of the left ventricle. In three dogs, silver-silver chloride wick electrodes were used for direct epicardial exploring electrodes.

Simultaneous records were taken with exploratory intracavitary and direct or indirect epicardial leads, using two Sanborn Cardiettes, or a Cardiette and a Visocardiette. These records were coordinated frequently. The sensitivity of the recording system was so modified that each millimeter of deflection represented 1.0 or 2.0 millivolts in the finished record; that is, one centimeter of deflection equalled 10 or 20 millivolts. This was accomplished with the aid of a simple attenuator.* The indifferent electrode was a Wilson central terminal, although comparison of tracings made with the Wilson central terminal or with any of the extremities as the indifferent electrode showed no significant changes of voltage or configuration when direct exploratory leads were employed. The polarity was arranged in all experiments so that an upward deflection indicated positivity of the exploring electrode.

Various methods were employed to produce thermal changes. Hot (45 to 60° C.) or cold (5 to 8° C.) saline was injected in 20 c.c. amounts into the cavity of the ventricle within one to three seconds. The temperature of the saline was noted as it entered the syringe; undoubtedly the temperature had fallen or risen by the time the solution reached the ventricular cavity. To avoid the T-wave changes which consistently occur after the heart has been stopped with acetylcholine or vagal stimulation,[3,25] we did not change the basic rhythm of the heart. Hot or cold solutions were injected into the cavity, and intra- and extracavitary potentials were recorded continuously. The effects were immediate, with rapid recovery occurring in ten seconds to two minutes. It is safe to assume that in our method of injecting cold or hot solutions against the endocardium of the apex, without the heart being stopped, that the electrocardiographic changes are due to local changes in that region. The tip of the electrode was within 1.5 cm. of the endocardium of the ventricular apex, and the solution injected under pressure impinged against the endocardium. The decrease of the height of the T wave in the epicardial lead with endocardial heating, for example, cannot be accounted for by conduction of heat from the endocardium to the epicardium, so that the epicardial lamina under the electrode becomes warmer than in the control. If that were the case, then the T wave in the epicardial lead should become taller, since it has been well established that heating the epicardium causes tall T waves to occur. Actually, when the endocardium was heated, the T wave in the epicardial lead became inverted.

In two dogs, localized posterior endocardial cooling was produced by the injection of cold solution through a needle which was introduced through the anterior basal wall of the left ventricle with the tip of the needle 1.5 cm. from the endocardial surface of the left ventricular basal wall. Direct epicardial leads were recorded from the midportion of the anterior wall of the left ventricle.

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*We are indebted to Arthur Miller, Sc.D., Chief Electrical Engineer of the Sanborn Company, for suggesting this attenuator.

Control experiments consisted of the intracavitary injection of similar amounts of saline of body (rectal) temperature. Consistently, there was no change in the intracavitary or epicardial leads. Therefore, the effects of hot or cold intracavitary injection cannot be attributed to the effect of ventricular distension or of a sudden increase of intraventricular pressure. In the experiments of Byer,[3] large quantities of fluid (50 c.c.) were used.

Epicardial thermal changes were produced in dogs with intact chests by spraying of the intact epicardium with 20 c.c. of hot or cold saline through a large needle introduced into the fourth or fifth intercostal space near the left parasternal line. Precautions were taken to prevent pneumothorax during this procedure. Precordial leads and intracavitary leads were used in these experiments. In open chest preparations, with the heart suspended in a pericardial cradle, the temperature of the ventricular surface was altered by local application of ice cubes, or by a fine stream of cold or hot solution.

Control electrocardiograms were always taken when the electrodes in the right and left ventricles were in place, to exclude endocardial pressure injury, indicated by elevation of the RS-T segment.[10,5] In addition, limb leads, unipolar limb leads, and precordial leads were taken. Records in each experiment were taken before, continuously during the thermal changes, and at varying intervals thereafter. Because of the transient nature of the effects, repeated experiments could be performed on the same animal. The amount of fluid introduced into the blood stream by intracavitary injections during the experimental period of one to five hours apparently produced no deleterious effects. Neither pulmonary edema nor marked changes in blood pressure occurred.

RESULTS

1. *Effect of Intracavitary Cooling.*—Cooling (a) of the endocardial portion of the apex of the left ventricle was produced in nine experiments in five dogs; (b) of the apical right ventricular endocardium, in four experiments in two dogs; and (c) of the endocardial surface of the posterior basal portion of the left ventricle, in four experiments in two dogs. The temperature of the saline in the syringe before injection ranged from 5 to 8° centigrade.

In all experiments primary T-wave changes[26] occurred in epicardial and intracavitary leads without significant QRS-T area changes. The results were consistent and may be summarized as follows: In every instance electrical systole (Q-T interval) was prolonged, up to 46 per cent of the control value. Rate (R-R interval) did not change significantly except when cold solution was injected into the right ventricle. Then slowing was immediate.

The changes in the intracavitary complexes were the same with cooling of the apical or posterior basal endocardium. The QS complex decreased in depth but increased in duration, so that there was not a significant net change in the QS area. However, there were significant T-wave changes. T waves became wider, and deeply negative, with marked increase of the RST-T area.* If the control T wave in the cavity were upright, indicating some cooling effects of the

*We have recently produced similar changes in man by the injection of physiological saline at room temperature against the right ventricular endocardium.

exposed epicardial surface (in which case the epicardial lead showed negative T waves), cooling the endocardium resulted in T waves which became negative (Fig. 1). If the control T waves were negative, they became more negative (Fig. 2). In no experiments were there significant deviations of the RS-T segment ascribable to the intracardiac injections.

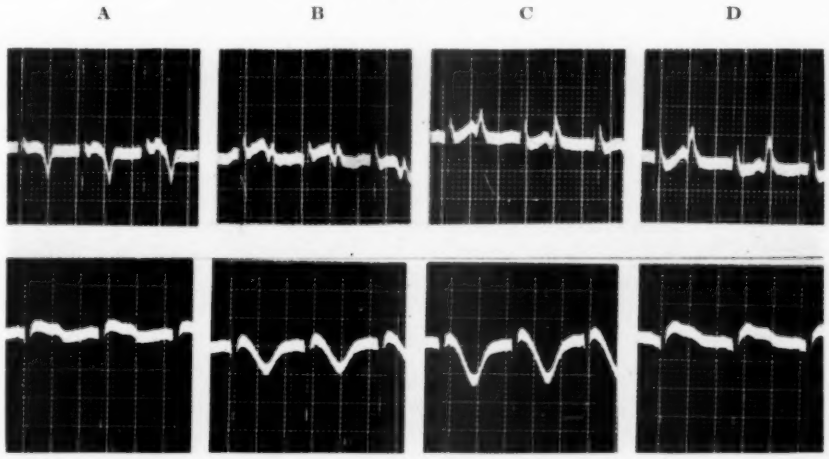

Fig. 1.—Effect of cooling endocardium of the left ventricle on intracavitary and epicardial leads.

Upper strip: Control record (*A*) shows negative T wave in direct epicardial lead, due to cooling of epicardium. *B*, *C*, and *D* are one, two and three seconds, respectively, after intraventricular injection of 20 c.c. of 6° C. isotonic saline, and show stepwise change of direction of T wave.

Lower strip: Another preparation. Control record (*A*) in left ventricular cavity (× 20 N); *B* and *C*, one and three seconds, respectively, after endocardial cooling; *D*, five seconds later. Between *A* and *C* there was an increase of 248 per cent in the net QRS-T area, due mainly to large negative T waves. See text.

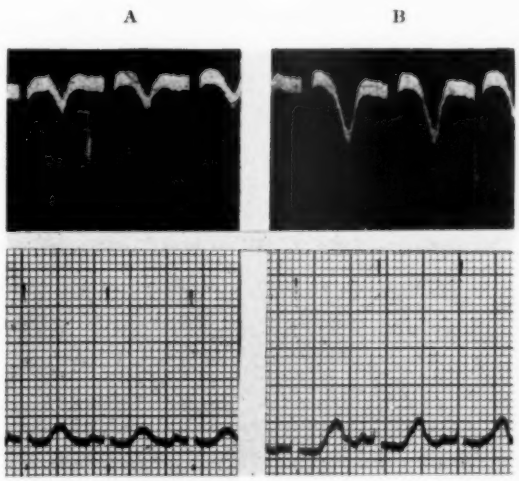

Fig. 2.—Electrical changes occurring within the left ventricular cavity (upper strip) and over the apex of the left ventricle (lower strip), following the cooling of the endocardial portion of apex of left ventricle. In row *A* are the control records, and in row *B* the record of the period during which the endocardium was being cooled. The area of QRS-T increased 51 per cent and 30 per cent, respectively. Discussed in text.

The changes in the direct or indirect epicardial leads depended upon the location of the exploring electrode in reference to the area cooled. With cooling of the apical left ventricular endocardium in the superjacent epicardial leads, there was no change or a slight increase in the height of the R wave, with widening of the QRS complex. T waves became wider, and higher, with an increased area, disproportionate to the change, if any, of the QRS complexes. Significant changes of the RS-T segment did not occur. Upon recovery, T waves returned to original values in all but two experiments, where they were slightly smaller than in the controls. When the endocardium of the apex of the right ventricle was cooled, precordial leads over the apex of the interventricular septum showed

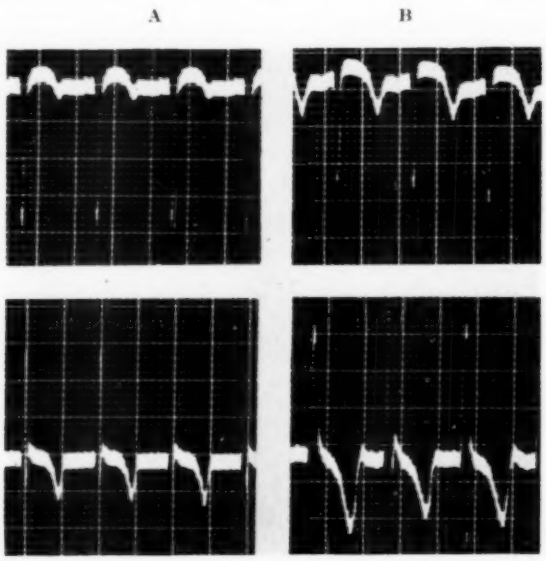

Fig. 3.—Effect of cooling endocardium of basal portion of left ventricle. Note that the T wave became more negative both in the left intraventricular tracing (upper strip) and in the direct epicardial tracing from the anterior wall of the left ventricle (lower strip). Discussed in text.

the appearance of a slightly deeper S wave, and the R wave increased slightly, or did not change. Electrical systole was prolonged. There was an increase in amplitude and duration of the T wave, similar to that in left apical endocardial cooling.

In the experiments where the endocardium of the basal portion of the posterior left ventricle was cooled, the R wave in the anterior epicardial lead became taller and the S wave deeper. However, the T wave in this lead became markedly inverted, similar to the intracavitary lead (Fig. 3). This result is similar to that obtained by Byer and associates.[3]

Fig. 4 demonstrates the similarity of results obtained by cooling the endocardium and by heating the epicardium; that is, upright T waves in the epicardial leads, and large negative T waves in the cavity, the latter not shown in this figure.

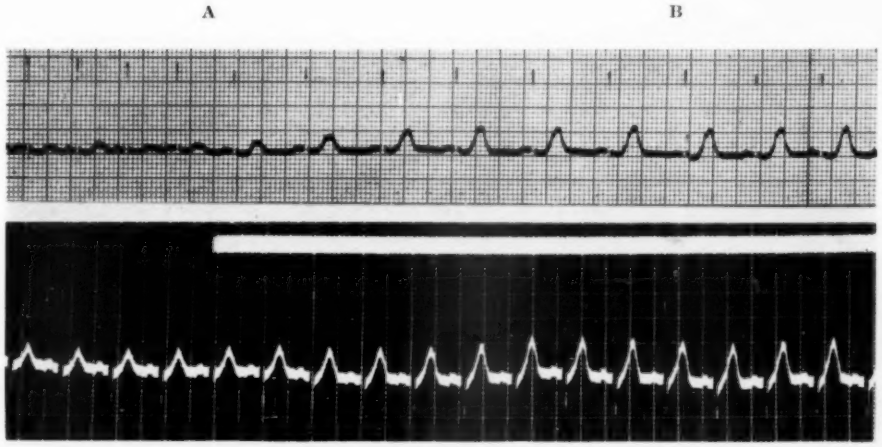

Fig. 4.—Similarity of effect of cooling the endocardium (upper strip) and heating the epicardium (lower strip) on the T waves of apical precordial lead. Two different dogs were used. The area of QRS-T increased 42 per cent and 109 per cent, respectively, between Complexes *A* and *B*. Discussed in text.

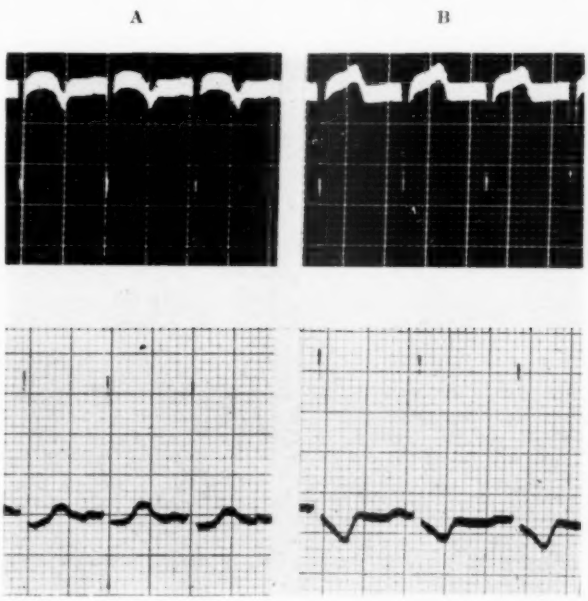

Fig. 5. Effect of heating endocardium of left ventricle on intracavitary (upper strip) and epicardial (lower strip) leads. The T waves became positive in the cavity and negative on the epicardium, with a decrease of 84 per cent and 82 per cent, respectively, of the area of QRS-T.

2. *Effect of Intracavitary Heating.*—Heating of the endocardial aspects of the apex of the left ventricle was produced in nineteen experiments in four dogs, with consistent results. The rate did not change significantly; the duration of electrical systole decreased, with a maximum shortening of 22 per cent of the control value. Net QRS-T areas changed significantly, with T waves becoming upright in intracavitary leads, and markedly inverted in epicardial leads, without proportionate QRS changes (Fig. 5).

3. *Effect of Cooling of Left Ventricular Epicardium.*—Cooling of the epicardial surface of the left ventricle was produced in seventeen experiments in five dogs. The effects were transient, subsiding spontaneously in less than three minutes. Local application of heat in the region previously cooled hastened recovery. The heart rate did not change significantly. The Q-T interval became prolonged. The most remarkable changes were the primary T-wave changes. In the intracavitary leads, the T waves became upright and broad, and in the epicardial leads, negative and broad. There was no significant change in the duration or amplitude of the QRS complex.

In Fig. 6 the effect of epicardial cooling is shown, where the control records show an upright T wave in the epicardial lead, and a negative T wave in the

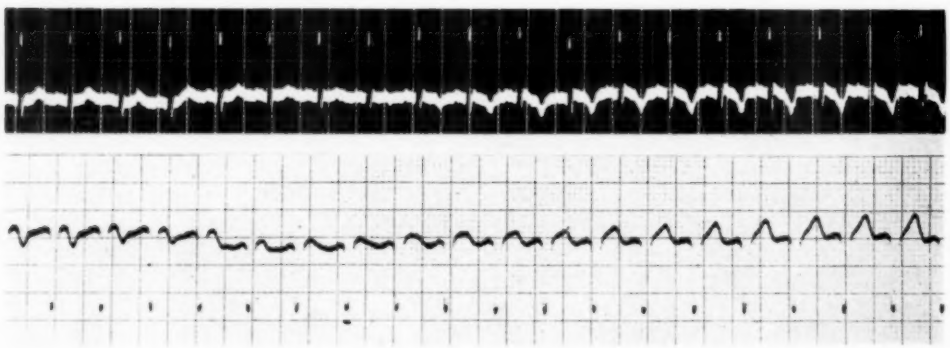

Fig. 6.—Effect of cooling of epicardium on direct epicardial (upper strip) and intraventricular leads (lower strip). Note progressive change in direction of T wave, which became negative in the epicardial lead, and positive within the ventricle.

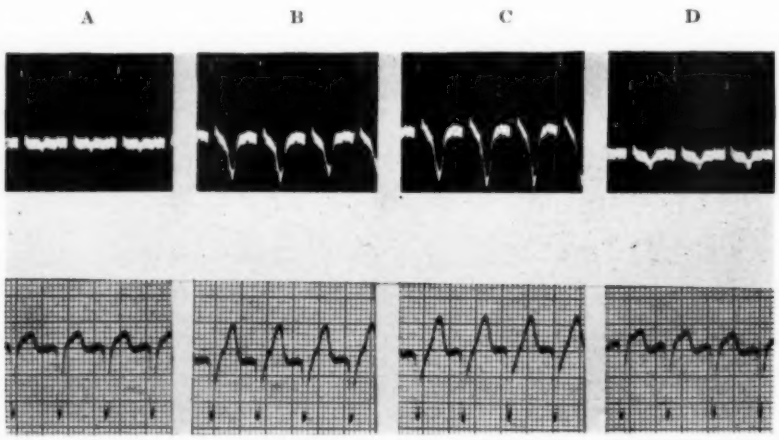

Fig. 7.—Effect of cooling left ventricular epicardium on leads in cavity of left ventricle (lower strip) and over apex of left ventricle (upper strip). *A* shows control records, and *B*, *C*, and *D* were taken three, five, and fifteen seconds respectively, after the epicardium was cooled. T waves become more positive within and more negative outside of the ventricle, with an increase of area of QRS-T of 280 per cent and 170 per cent, respectively, between *A* and *B*.

intracavitary lead. With cooling there is a progressive change from the positive value to zero and then to a large negative value in the epicardial leads, and the opposite changes occur in the cavity.

In Fig. 7 the effect of epicardial cooling is shown, where the T waves in the control records are negative in the epicardial lead, and positive in the cavity. Further cooling increases the negativity and positivity of the T waves in the respective leads.

4. *Effect of Heating Left Ventricular Epicardium.*—Heating of the epicardial surface of the anterolateral aspect of the left ventricle was produced in eleven experiments in four dogs. In all experiments there were primary T-wave changes, with the T waves becoming taller in the epicardial leads, and markedly inverted in the ventricular cavity (Fig. 8). The Q-T interval shortened slightly in eight experiments, and increased (0.01 to 0.02 second) in three experiments.

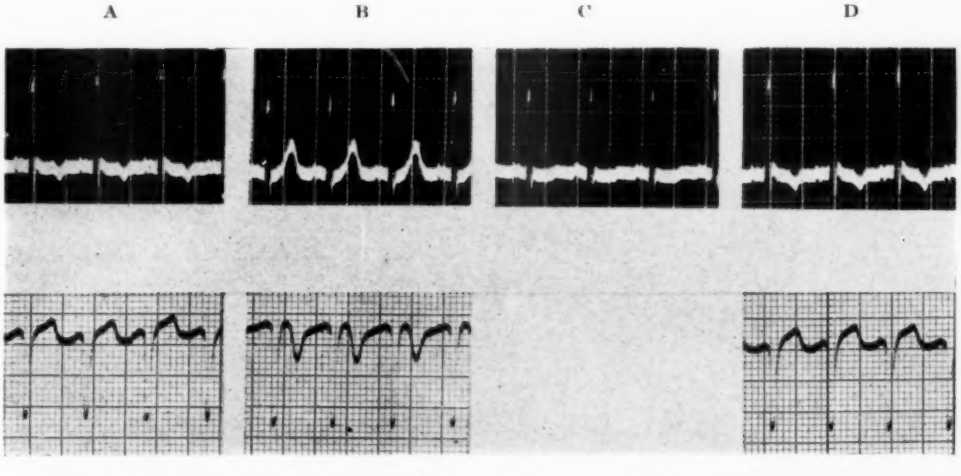

Fig. 8.—Effect of heating left ventricular epicardium on precordial (upper strip) and intracavitary (lower strip) leads. Row *A* shows control records, and *B*, *C*, and *D* were taken, respectively, one, three and five seconds later. Note the marked change in the direction of the T wave, positive in the precordial lead and negative in the ventricle; a change of area of QRS-T of 72 per cent and 263 per cent, respectively. Discussed in text.

The effect of heating various portions of the epicardium of the left ventricle, and the effect of cooling various parts of the left and right ventricle on an electrode in the left ventricular cavity were tested in two dogs. Consistently, it was found that heating any part of the left ventricular epicardium, specifically, the apical, anterior, basal, or posterior aspects, produced large, negative T waves in tracings recorded in the cavity subtending that area. Cooling any part of the epicardium of the right ventricle or left ventricle produced positive T waves in the cavity. The magnitude of the effect of cooling was dependent upon the size of the area cooled. In the latter experiment the effect of cooling an area 2.5 by 2.5 cm. with an ice cube was significantly greater than cooling an area 1.5 by 1.5 centimeters.

Although an intracavitary lead will show the same T-wave change with a thermal change of any part of the epicardium, in extraventricular leads (limb or epicardial) this does not obtain. The importance of the orientation of the exploring electrode to an epicardial area cooled or heated has been amply demonstrated by previous investigators.[6,14,16,18-20,27] Thus, cooling of the base causes a negative T wave in the superjacent epicardial lead, and a taller T wave at the apex, or in any leads subtending the apical portion of the heart. Contrariwise, cooling of the apex causes negative epicardial T waves at the apex, and positive T waves at the base. Heating of the apical epicardium produces locally tall T waves; heating of the base produces negative T waves at the apical epicardial lead.

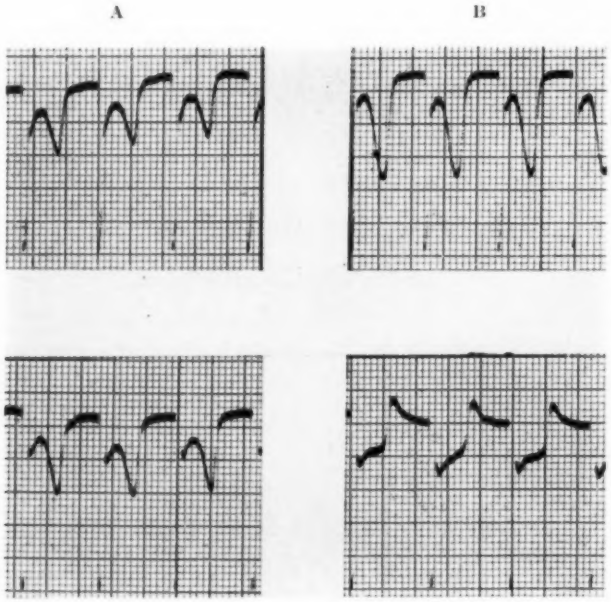

Fig. 9.—Effect of heating and cooling an area of subepicardial injury on intraventricular potentials. Upper row: *A* shows control record with RS-T depression due to an area of epicardial pressure injury 3 by 3 cm. over the apex of the left ventricle. *B* shows the effect of heating the injured area; the RS-T depression persists, but the T wave is markedly more negative, and there is an increase of the area of QRS-T of 52 per cent. Lower row (*A*) shows control record with RS-T depression due to subepicardial injury. *B* shows the effect of applying cold to the area of injury. The T wave became upright, although the RS-T depression persisted. The area of QRS-T decreased 25 per cent. Discussed in text.

5. *Miscellaneous Observations.*—In one dog, six experiments were performed showing the effect of heating and cooling an area of subepicardial injury. Epicardial pressure injury was produced in an area approximately 3 by 3 cm., over the apical anterior left ventricle. The electrode in the left ventricle recorded marked depression of the RS-T segment. In a previous study[10] negative displacement was consistently found in the cavity after subepicardial injury. Heat was applied to the area of injury, and the T waves within the cavity became markedly negative and the electrical systole shortened. After several minutes the T wave returned to its control value, with residual RS-T depression. Cold

solution applied to the area of injury produced upright T waves, although the RS-T segment remained depressed. The Q-T interval became prolonged (Fig. 9).

Thus, even in the presence of subepicardial injury, as manifested by RS-T depression in the cavity, heat and cold accelerated and retarded, respectively, repolarization when applied to the area of injury. The direction of the T wave in the cavity was negative after epicardial heating, and positive after epicardial cooling, changes similar to those occurring in the uninjured heart.

Alternation of the T wave, more correctly stated the ST-T complex, occurred in several dogs, without alternation of the QRS complexes (Fig. 10). This phenomenon was observed in intra- and extraventricular leads, usually at the end of a long experiment. In a previous communication[10] it was reported that similar alternation occurred after a large area of the right ventricular wall was charred, and preceded spontaneous ventricular fibrillation. In other experiments, to be reported later, alternation of the RST-T complex occurred regularly within two or three minutes after coronary occlusion.

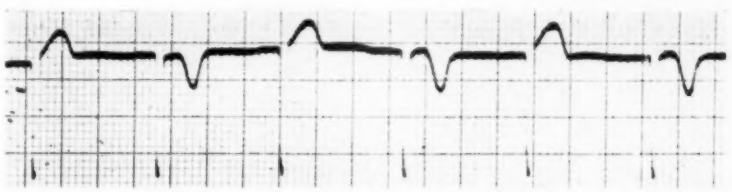

Fig. 10.—Alternation of the RST-T complex without QRS alternation. This record was obtained from within the cavity of the left ventricle two minutes after the injection of 20 c.c. of 60° C. physiologic saline. Spontaneous ventricular fibrillation occurred soon thereafter. Discussed in text.

DISCUSSION

The results of these experiments can be readily explained by a logical extension of the classical membrane theory as applied to a heart immersed in an extensive conducting medium. Further details can be obtained by reference to other work.[10,29,30]

The classical membrane theory postulates that the atria and ventricles are each a syncytial cell bounded by a semipermeable membrane.[10] In the resting state, the cell is polarized, with an equilibrium between the positive charges on the outside of the membrane and the negative charges on the inside of the membrane. During activity, the permeability of the cell surface is altered; there is a decrease in the impedance (electrical resistance of the cell surface), and the ions which are responsible for the polarized state of the resting "polarized" cell migrate and the cell becomes depolarized. The difference in potential between the inside and outside of the cell disappears wholly or in part. The process of depolarization (excitation, accession) takes time, and has an asynchronous but fairly typical topographical spread. When all parts of the cell are activated, the cell surface is completely depolarized, and as in the polarized state, all parts of the cell surface are at the same potential. Hence, the RST-T segment is near zero potential. The process of repolarization which follows is slower than the process of depolarization. The T wave is due to the electrical force produced by

the return of the ventricles from the active to the resting state. The topographical pattern of repolarization in the cell is not usually identical with that of depolarization. If it were identical, and if the duration of electrical systole were precisely the same in all parts of the cell, then potential differences during repolarization would be the opposite in sign to those in the state of depolarization, and the area subtended by it would be equal to that subtended during depolarization. When the cell is in an extensive conducting medium, during depolarization and repolarization, a hypothetical surface at the junction between depolarized and polarized portions of the cell can adequately account for the electrical field created in the medium. The series of doublets lining this theoretical surface can depict the origin of the electrical field. The negative poles of these doublets are on the side of the surface toward the depolarized portion of the cell, while the positive poles are toward the polarized portion of the cell, and the intensity of the charge on the theoretical surface is equal to the intensity of the charge on the polarized part of the cell surface.[29-35]

In the intact unanesthetized or lightly anesthetized man or dog, in the intracavitary electrocardiogram of both ventricles (dog), right ventricle (man), and in the right arm unipolar lead, the major QRS complex is negative, as is the T wave. The epicardial or precordial leads over the left ventricle show upright QRS and T complexes. We can safely say that if the order of repolarization were predominantly in the same order as depolarization, that is to say, subendocardial muscle before subepicardial, the T wave would have a sign and direction opposite to that of the QRS complex (upright in the cavity of the ventricle, and inverted over the epicardium). Since the QRS and T complexes are normally in the same direction, the subepicardial myocardium must recover earlier than subendocardial muscle.[36] There is some theoretical evidence[37] that during systole the rise of pressure within the subendocardial lamina is great enough to stop its blood flow, but in the subepicardial layers flow continues. This may be a factor in explaining the lack of uniformity of duration of the excited state in the subepicardial and subendocardial layers of the ventricle.

Regardless of the pattern of topographical spread, whether apex before base or not, the effective direction of depolarization is always from the endocardium to epicardium. Otherwise, within the cavity of the ventricle, positive deflections would be encountered other than the small positive deflection in the right ventricle which is derived from the earlier depolarization of the upper part of the left side of the septum. In the left ventricle, the QRS complex is of the QS variety. In only one of seventy-five dogs have we observed a positive deflection in the left ventricle, although the RS complex is the usual type in the upper right ventricular cavity. Similarly, regardless of the pattern of the topographical spread of repolarization, if the T wave is negative in the cavity, the predominant direction of repolarization is from subepicardium to subendocardium. If the T wave is positive in the cavity, the opposite obtains. In the situations where the T wave is inverted in the epicardium, we found that the T wave is upright within the cavity. In seventy-five dogs control tracings have been made at various levels of the ventricular and atrial cavities, and the direction of the T wave in the cavity has been found to be exactly opposite that on the epicardium. Under

experimental conditions, the direction of the T wave may vary in different parts of the same cavity. In several dogs we have produced localized cooling of the anterior basal left ventricular epicardium, and in the epicardial leads from this area the T wave was inverted. An intracavitary electrode in the tip of the ventricle had the usual normally inverted T wave. However, when the tip of the catheter electrode wave moved to a position subjacent to the cooled area, the T wave was upright. This demonstrates the importance of the spatial orientation of the electrode to the area of altered repolarization.

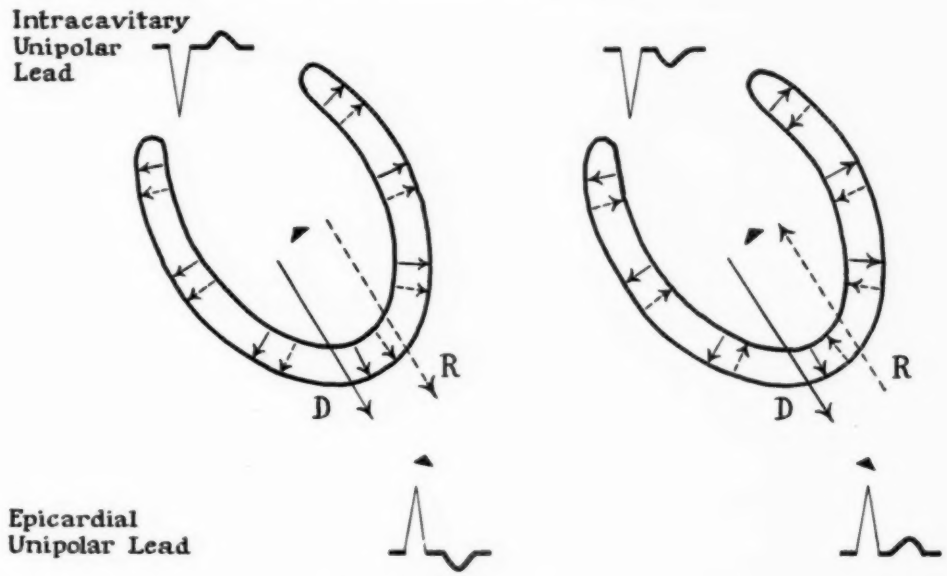

Diagram I.—Discussed in text.

In Diagram I, the relation of the direction of the T wave in the cavity and on the epicardium is shown to be related to the order of endocardial-epicardial repolarization. To simplify the discussion, the diagrams represent only the left ventricle. The QRS complexes are assumed to remain constant. T waves are upright in that lead where the nearest myocardium recovers before distant points. Stated otherwise, the T wave is negative whenever the myocardium nearest the exploring electrode recovers later than other areas.

In Diagram II, instead of using a single cell, as is customarily done, we are dealing with a piece of heart muscle of a shape similar to that of the idealized cell, extending from the endocardium to the epicardium. The exploring intracavitary (essentially endocardial) electrode is in the region where depolarization starts, and will be in a negative field, just as the epicardial electrode will be in a relatively positive field. The indifferent electrode is a Wilson central terminal. After depolarization is completed, the heart is in an electrically quiescent state for a variable length of time. The process of repolarization which follows is slower. In the left-hand column repolarization begins at the endocardium.

Negative charges are facing the epicardial electrode, and positive charges, the endocardial electrode; as the intensity of polarization increases, the effect is to produce a positive deflection in the endocardial tracing, and a negative deflection in the epicardial tracing. In the right-hand column of the same diagram, repolarization begins at the epicardium. In this instance, positive charges are facing the epicardial electrode, and negative charges, the endocardial electrode, producing upright, positive T waves in the epicardial lead, and negative T waves

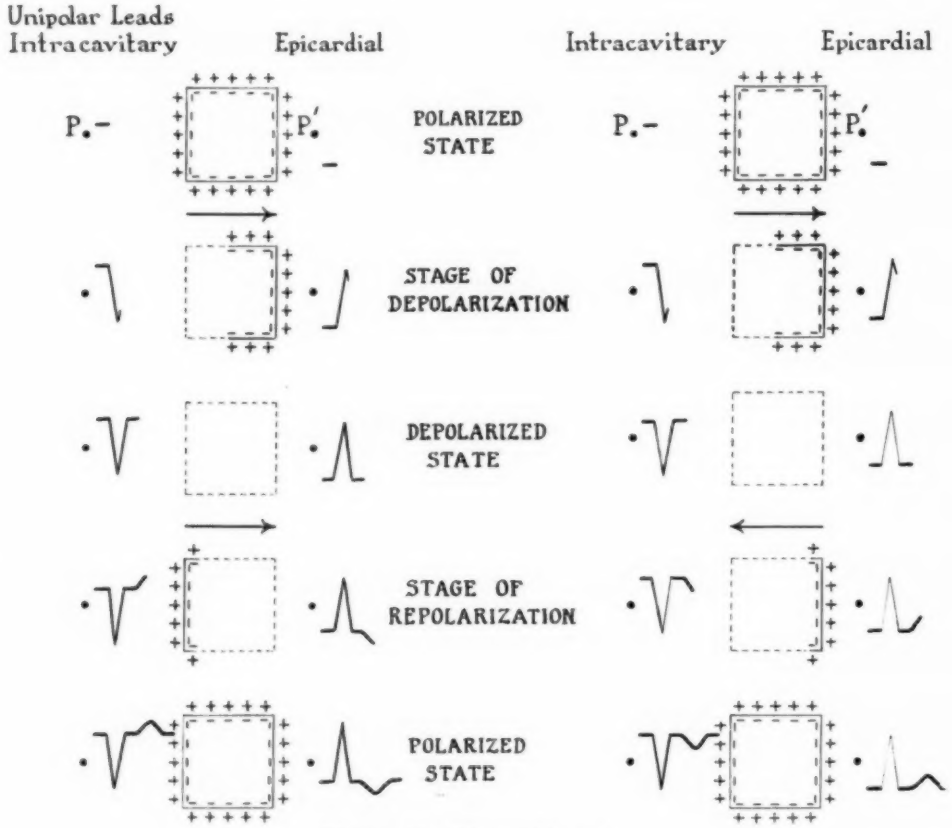

Diagram II.—Discussed in text.

in the endocardial. We realize that this is a simplification of the true situation; for example, in the latter instance it is probable that the endocardial muscle had begun its repolarization in Step 4, but the intensity of polarization is so much greater at the epicardial region that the net effect of the two fields results in positivity at the epicardium and negativity at the endocardium.

The theory which has been outlined can now be applied to the results of our experiments. It has been long known and frequently restated[3,19,26,28,39] that local cooling of the myocardium causes a delay of recovery from the refractory state, and that cooled surfaces are negative relative to an uncooled surface. The con-

verse obtains also: warming of the ventricles shortens the local duration of the excited state at the part warmed, and heated surfaces are relatively positive to uncooled areas. In other words, unheated areas are negative relative to heated surfaces. Burdon-Sanderson and Page[16] noted in 1880 that in "local warming of muscle in the region of one electrode, the capillary electrometer record which resulted from stimulation of the muscle was modified in just that sense which would be predicted as the result of hastening the termination of the excited state under the warmed electrode."

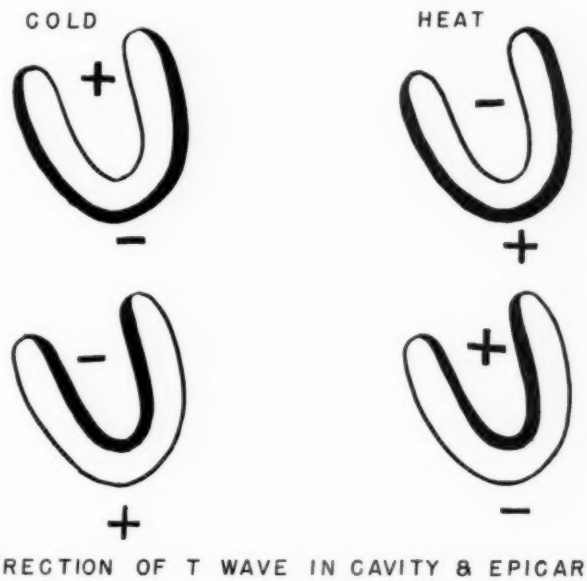

Fig. 11.—Diagrammatic representation of the effect of thermal changes in various locations of the T wave. The blackened areas in each figure locate the zone of altered repolarization. The plus sign means positive T waves and the minus sign, negative T waves. Heating of the epicardium and cooling of the endocardium produced T waves of similar direction; likewise cooling of the epicardium and heating of the endocardium produced T waves of similar direction. Discussed in text.

In Fig. 11 a schematic recapitulation of our experimental results is presented. Tracings from electrodes nearest the area of cooling have negative T waves. From the previous discussion it is apparent that repolarization begins at distant areas, and proceeds toward the electrode which subtends the retarded zone. As represented in the left-hand column of Fig. 11, cooling of the endocardium caused negative T waves in the cavity, and positive T waves on the epicardium; and cooling of the epicardium produced negative T waves in the area cooled, and positive T waves in the cavity.

However, in another situation, we note that negative T waves are inscribed, that is, where the repolarization at distant points is accelerated; thus, heating of the endocardium causes upright T waves in the cavity, but negative T waves in the epicardium, and heating the epicardium produces even taller T waves on the epicardium and more deeply negative waves in the cavity. Thus, in terms

of the membrane theory, heating an area increases the intensity and rate of repolarization, so that electrodes immediately adjacent to or facing this area will be in a relatively and absolutely more positive field than they would be at a distant point. Likewise, electrodes distant to the area of accelerated repolarization will be in a relatively more negative field, and negative T waves will be recorded.

Thus, in an epicardial lead, negative T waves may mean (a) that the subepicardial myocardium immediately subjacent to the electrode has repolarized tardily, (b) that the endocardial muscle immediately subjacent has had accelerated repolarization, (c) that the subendocardial muscle of the contralateral wall has tardy repolarization (as shown by the experiments where cooling of the posterior endocardium caused negative T waves on the anterior epicardium), or (d) that there has been accelerated repolarization of the subepicardial myocardium of the contralateral wall (the latter possibility is a theoretical one which we have not tried to produce experimentally). A positive T wave in an epicardial lead may mean that there is (a) accelerated repolarization in the subjacent subepicardial layers, (b) retarded subjacent subendocardial repolarization, or (c) retarded subepicardial repolarization of the contralateral wall (tall T waves in the anterior precordium with posterior infarcts).

As has been mentioned in the introduction, the modern concepts of electrocardiographic theory are such that these changes could be anticipated. The use of the intracavitary electrodes has confirmed the correctness of these views.

The T-wave changes that occurred in our experiments of cooling and heating are primary T-wave changes and are significant. Although the form of the T wave is dependent to a large extent upon the form of the QRS complex, it may vary independently. When large changes occur in the QRS areas, the T deflection may be a thoroughly unreliable index of the magnitude of the net electrical effect.[3] Therefore, it is necessary to compare the net QRS-T areas of complexes. The difference between control values and values after thermal changes is an index of the magnitude of the changes. In our experiments, the magnitude of primary changes has been calculated in microvolt-seconds and Ashman units, and expressed in per cent change in area of the QRS-T.*

The recent attempt of Nahum and Hoff[14] to explain the T wave as a result of the interference of the terminal portion of dextro- and levocardiograms is an extreme oversimplification of the problem. Although in the use of limb leads alone, the picture may be a very rough approximation of the summation of two monophasic curves, in the use of precordial and intracavitary leads this concept is inadequate. A record taken over the anterior surface of the apex of the left ventricle, with the central terminal as an indifferent electrode, would need to take into account several pairs of monophasic curves: a pair from the anterior and posterior walls of the left ventricle, from the subendocardial and subepicardial muscular lamina of the anterior and posterior walls each, from the right and left sides of the interventricular septum, and from the right ventricular walls. A variety of modifications of the levocardiogram, for example, can be produced

*We are indebted to Dr. M. Dolgin for assistance in making these measurements.

by the same thermal change of the subendocardial or subepicardial lamina of anterior, posterior, or lateral parts of the left ventricle. The direction eof th T wave will be dependent upon the orientation of the exploring electrode to the modified area.

CLINICAL APPLICATIONS

The experimental results which have been presented give direct proof of the theoretically expected effect of the rate of repolarization on the T wave of the electrocardiogram. Our results also show the fundamental importance of the spatial relationship of the exploring electrode to the modified area. These two points may be used to clarify the electrocardiographic findings in such clinical conditions as pericarditis and myocardial infarction.

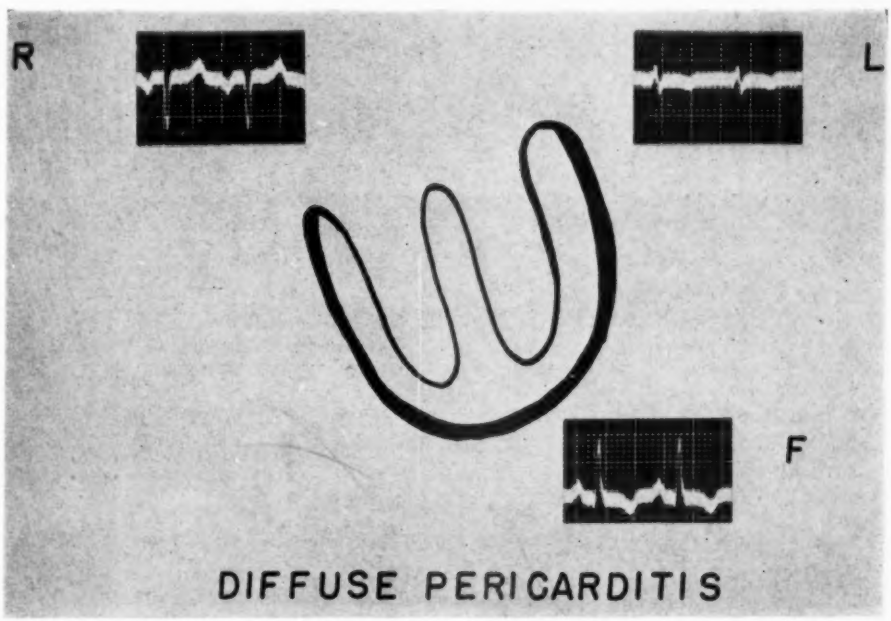

Fig. 12.—Electrocardiogram of 31-year-old woman with diffuse pericarditis. Diagram shows laminar subepicardial involvement. The T waves are negative in the left arm and left leg unipolar leads, and in the precordial leads (latter not shown). Note positive T wave in right arm unipolar lead. Discussed in text.

In pericarditis, electrocardiographic changes occur when the subepicardial myocardium is involved. In the latter stages of diffuse pericarditis, negative T waves are found in the precordial and unipolar left arm and left leg tracings. However, the right arm lead, which records potentials similar to a true intracavitary lead, shows positive T waves. In Fig. 12 the electrocardiogram of a 31-year-old Negro woman with acute diffuse pericarditis shows negative T waves in aV_L, aV_F, and all precordial leads. In aV_R the T waves are positive.

In anterior myocardial infarction, the anterior precordial electrodes record large, negative T waves, which is evidence of delay in repolarization predomi-

nantly of the subepicardial myocardium of the anterior wall. Conversely, typical posterior myocardial infarction results in tall T waves in the anterior precordial leads. In the afore-mentioned instances of infarction and of pericarditis, the direction of the T wave is determined by the location of the exploring electrode in relation to the area of retarded repolarization. When the electrode is near this area, the T wave is negative; when it is distant, and separated by muscle of relatively faster repolarization, the T wave is upright.

A separate communication will deal with the application of this concept to the interpretation of the direction of the T-wave changes in experimental coronary occlusion and in human exercise tolerance tests.

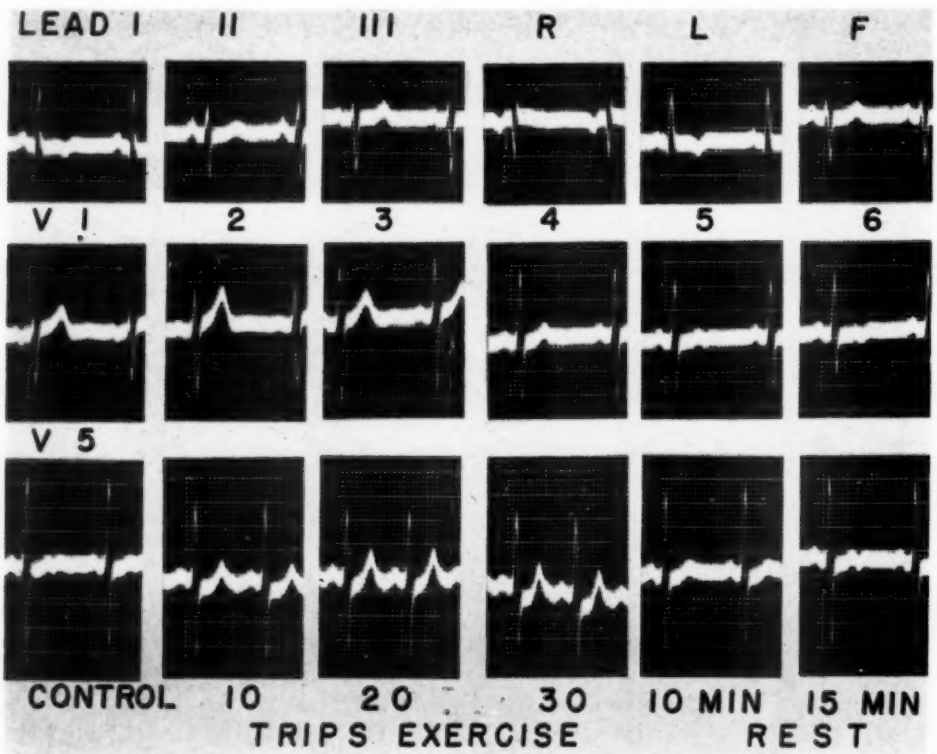

Fig. 13.—Electrocardiogram of 40-year-old physician with angina pectoris. Upon exercise, the T wave in the precordial lead became upright. Discussed in text.

Prinzmetal and co-workers[40] have recently shown that immediately after occlusion of the anterior descending branch of the left coronary artery of the dog's heart, the endocardial side of the ischemic myocardium of the left ventricle receives a definitely poorer blood supply than the subepicardial portion. It would be expected from this that during exercise the heart with coronary sclerosis of the left anterior descending artery would suffer greater ischemia in the subendocardium, and that this would be reflected in the anterior precordial lead by an increase of positivity of the T wave, and then by a depression of the RS-T

segment. In the great majority of positive or abnormal exercise tolerance tests, the latter has been reported.[41] A review of our records has disclosed many instances of the former. One illustration will be given here. Fig. 13 is the record of a 40-year-old physician with severe angina pectoris, and shows left axis deviation, sinus rhythm, and inverted T waves in Leads V_4, V_5, and V_6. Upon exercise (twenty trips over standard steps) the patient developed angina pectoris, and Leads V_4, V_5, and V_6 showed upright T waves and slight depression of the RS-T segment. This test indicates coronary insufficiency. Our interpretation is that the control record (inverted T wave in Leads V_4, V_5, and V_6) indicates delayed repolarization of the anterior subepicardial muscular lamina. With exercise, there was coronary insufficiency with predominant subendocardial ischemia. This resulted in a slowing of subendocardial repolarization which was greater than the slowing of the subepicardial repolarization, and, therefore, an upright T in the precordial leads. The associated RS-T depression confirms the localization of predominant ischemia in the anterior wall subendocardial layers, since in a previous study[10] it was shown that RS-T depression in the anterior epicardial lead could be produced by anterior subendocardial injury.

SUMMARY

The effects of cooling and heating the endocardium and epicardium have been studied by the use of intra- and extraventricular exploring unipolar leads.

Direct evidence has been obtained that changes in the electrical state of the endocardial muscular lamina modify the form of the electrocardiogram. Changes in the T wave can be produced by changing the rate and order of endocardial-epicardial laminar repolarization.

Negative T waves occurred where the exploring electrode subtended areas which had relatively or absolutely retarded repolarization; positive T waves occurred where the exploring electrode subtended areas which had relatively or absolutely accelerated repolarization.

It was found that negative T waves occurred:

A. *In the cavity* (1) when the endocardium was cooled; (2) when the endocardium was not altered, but the epicardium was heated.
B. *On the epicardium or precordium* (1) when the epicardium immediately under the electrode was cooled; (2) when the endocardium subjacent to the epicardial exploring electrode was heated; (3) when the endocardium of the opposite wall was cooled.

It was found that positive T waves occurred:

A. *In the cavity* (1) when the endocardium was heated; (2) when the epicardium was cooled.
B. *On the epicardium or precordium* (1) when the subjacent epicardium was heated; (2) when the subjacent endocardium was cooled.

The relation of these results to the modern concept of altered repolarization in an extensive conducting medium are discussed. The spatial relation of the

exploring electrode to a theoretical surface at the junction of the normal and altered areas is used to account adequately for the findings.

The practical value of these observations is discussed.

The present results confirm and extend previous observations on the contribution of the subendocardial myocardium to the electrocardiogram.

The authors wish to express their appreciation to Dr. Harold Feil for his review of the electrocardiograms, and for advice during this study.

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PLASMA PROTHROMBIN TIMES IN NORMAL HUMAN SUBJECTS. THE EFFECT OF CERTAIN FACTORS ON THE PROTHROMBIN TIME

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THE increasing use of prothrombin estimations of human plasma as a guide to Dicumarol and vitamin K therapy and as an aid in the diagnosis of hepatic disease makes it imperative that the limitations and variations in the prothrombin time determination be properly evaluated. Previous studies of prothrombin time variations in the normal human subject in different physiologic states have been limited in many respects.

The purpose of this study was to determine the effect of certain factors on the plasma prothrombin times[§] of normal individuals by the determination of (1) daily variations in normal subjects, (2) variations occurring in different normal subjects over a period of days, (3) variations obtained at different times during twenty-four hour periods, (4) the effect of exercise, and (5) the effect of a high-cholesterol diet.

A number of reports are available in the literature which record daily prothrombin times on whole and diluted plasma of normal individuals. Variations in method and technique, however, yield conflicting evidence and differing interpretations. Quick[10] in 1942 stated that "the prothrombin concentration in the blood of healthy adults is remarkably constant." Hause and Tocantins,[4] using the one-stage method of Quick, determined the prothrombin time of three healthy men for a period of fifty-three days. They obtained a mean clotting time of 19.49 seconds with a standard deviation of ± 0.953 second with whole plasma. In observations on women they found no consistent variation in the prothrombin level during any phase of the menstrual cycle. They observed that certain normal adults have consistently high prothrombin values. Cotlove and Vorzimer[3] studied the prothrombin levels of thirty-five normal control subjects using the Link-Shapiro modification of the Quick one-stage method with rabbit-lung thromboplastin and obtained a mean clotting time of 15.5 seconds on whole plasma with a standard deviation of ± 1.5 seconds. Aggeler and asso-

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§Determinations were made by the Link-Shapiro modification of the Quick technique[2,11]

ciates[1] performed tests on the blood of thirty normal subjects with human-brain thromboplastin, deriving a mean prothrombin time of 11.5 seconds with a standard deviation of ±0.73 second. The standard deviation was markedly increased in the diluted plasma both in the normal group and in the standard control subjects. However, they found no significant variation between the prothrombin values obtained in a group of normal subjects. Martin, Curfman, and Cavano[6] recorded the variations in prothrombin times obtained in a group of ninety-three normal people. The standard deviation for the whole plasma was ±0.6 second with a normal range of three seconds. The prothrombin times for dilute plasma were less consistent, having a standard deviation of ±10 seconds and a range of normal from 56 to 115 seconds. Application of the fibrinogen dilution technique developed by Nitshe, Gerarde, and Deutsch[8] to serial plasmas of normal human subjects demonstrated considerable differences in prothrombin activity as reflected by variations in prothrombin time.

The importance of the time of day and the relation of food intake to the drawing of the blood sample is disputed. Tanturi and Banfi[12] concluded that the prothrombin level in normal persons is constant and does not vary with the time of day. Levan,[5] however, noted that prothrombin determinations made after breakfast were higher than determinations made under fasting conditions. Meyers and Poindexter[7] found a tendency for the prothrombin time to drop after midnight in patients with coronary arteriosclerosis, but did not observe this to occur in six normal men. Using the Link-Shapiro modification of the Quick test with rabbit-brain thromboplastin, Martin, Curfman, and Cavano[6] ran serial determinations throughout the day. They found no significant difference in the blood samples taken before and after breakfast, but detected a consistent prolongation of the prothrombin times of the afternoon sample when compared with morning samples. Late evening specimens had somewhat shorter times than mid-afternoon, but longer than morning tests.

Since the early investigations of Cannon in 1914, the effect of exercise on blood coagulation has been variously interpreted. Meyers and Poindexter,[7] employing Link's modification of the one-stage method, could detect no change in prothrombin time following toe-touching exercises of five normal men and five patients recuperating from coronary occlusion.

Pronounced increases in prothrombin activity determined by the method of Quick were noted by Tocantins and O'Neill[13] in human and dog plasma after meals especially rich in protein. Warner, Brinkhous, and Smith[14] observed that great differences in the diets given to dogs produced variations in the prothrombin time but within the limits of experimental error. During the course of certain observations Pohle and Stewart[9] observed that a grossly lipemic plasma gave a short prothrombin time. Tests were run on three normal individuals who were on a low-fat diet for twenty-four hours, then repeated two hours after a diet containing 120 Gm. of fat had been given. The results suggested that a markedly lipemic plasma has a shorter prothrombin time than clear plasma. Martin and associates[6] were not able to demonstrate any difference in the whole plasma prothrombin times on blood samples taken two hours after a meal containing 20 to 30 Gm. of fat, or after a meal containing a higher fat content of 50 grams.

METHOD

All quantitative methods based on empirical rather than stoicheiometric relationships, can give reliable and reproducible results only when there is strict conformity to rigidly standardized manipulative conditions. This is especially true for the prothrombin time determination, since one is dealing here with the sensitive and variable processes of blood coagulation. If the procedure given below is followed carefully, reproducible results will be obtained.

Reagents and Solutions.—(1) Sodium oxalate, reagent grade and anhydrous, is prepared in a volumetric flask as a 0.1 molar solution by dissolving 13.4 Gm. in distilled water and diluting to 1,000 milliliters. (2) Sodium chloride, reagent grade, is prepared in a volumetric flask as an 0.85 per cent solution by dissolving 8.5 Gm. in distilled water and diluting to 1,000 milliliters. (3) Calcium chloride, of reagent grade and anhydrous, is prepared in a volumetric flask as a 0.025 molar solution by dissolving 2.77 Gm. in distilled water and diluting to 1,000 milliliters. (4) A thromboplastin-calcium chloride suspension is made by adding 0.1 Gm. of thromboplastin to 5.0 ml. of a 0.85 per cent sodium chloride solution in a 15 ml. centrifuge tube. The mixture is agitated thoroughly. The temperature of this suspension is maintained at 54 to 55° C. in a water bath for ten minutes with constant agitation, and then cooled to 25 to 26° centigrade. To the suspension 5.0 ml. of a 0.025 molar calcium chloride solution is added. The mixture is stirred for four minutes and centrifuged for four minutes at 1,700 revolutions per minute. The centrifuge is brought to a standstill slowly so as to avoid resuspending the flocculent precipitate. The slightly turbid supernatant solution is removed with a pipette and used in the determination.

Procedure.—To a test tube containing 0.5 ml. of a 0.1 molar sodium oxalate solution, 4.5 ml. of freshly drawn blood are added. This is quickly mixed. The oxalated blood is centrifuged at 1,700 revolutions per minute for ten minutes. The clear plasma is then transferred with a pipette to a test tube. The prothrombin time of the plasma should be determined as soon as possible after collection.

For the prothrombin time of whole plasma approximately 0.5 ml. of plasma is transferred into a 75 by 10 mm. test tube. If diluted plasma is to be used, 0.1 ml. of plasma is transferred into another 75 by 10 mm. test tube and diluted with 0.85 per cent sodium chloride solution. To obtain a plasma concentration of 12.5 per cent, 0.1 ml. of plasma is diluted with 0.7 ml. of saline. The whole plasma and diluted plasma samples can be conveniently mixed by firmly holding the test tube near the top with the thumb and index finger, and striking the lower end sharply with glancing blows using the index finger of the other hand. This accomplishes a thorough mixing without contamination. The whole and diluted plasmas are mixed thoroughly and placed in the constant temperature water bath at 37° centigrade.

From the thromboplastin-calcium chloride suspension 0.2 ml. is transferred into 100 by 12 mm. test tubes with a 0.2 ml. pipette of the type used in the micro determination of blood sugar. This suspension is blown into the test tubes and care is taken that the pipette is completely empty after each transfer. These tubes are placed in the rack beside the whole and diluted plasma samples in the

constant temperature bath. As soon as the contents of the tubes have reached the bath temperature, the prothrombin time of the plasma is determined as follows. The tube containing the whole plasma is shaken again and 0.1 ml. is transferred with a 0.1 ml. pipette to a tube containing 0.2 ml. of the thromboplastin-calcium chloride suspension. The plasma is quickly blown from the pipette and at the same time the stop watch is started. (The stop watch can be conveniently operated by a foot treadle.) The tube is tapped sharply to mix the solutions. This insures initiation of the clotting process uniformly throughout the solution. A small stirrer made of No. 22 nichrome wire with a small loop on the end is then introduced. If any small droplets are present on the sides of the tube they can be removed by passing the stirrer over them, thus making certain that all of the constituents are in the bottom of the tube. At this stage only two to three seconds should have elapsed since the time the plasma was added to the thromboplastin-calcium chloride suspension. The mixture is stirred so that the stirrer loop sweeps across the test tube from one side to the other at a rate of two times per second. *The end point (formation of clot) is that point at which the fibrin clot is sufficiently stable to be drawn to one side by the stirrer, thus bringing into view a clear area.* The clot is usually somewhat turbid, since the calcium oxalate formed upon calcifying the oxalated plasma is enmeshed in the clot. The formation of fibrids, which impart a viscous appearance to the solution before the clot forms, can be disregarded. Record the number of seconds required for clot formation. The same process is repeated, using the diluted plasma.

EXPERIMENTAL OBSERVATIONS

Normal Prothrombin Clotting Time.—Daily prothrombin clotting time determinations were investigated on twenty-five normal adult subjects* during periods of time ranging from ten to forty weeks. All values obtained in this study were recorded and all tests were run by three individuals experienced in this technique. A mean value of 15.8 seconds, with a standard deviation of 1.22 seconds was obtained as the prothrombin time on 828 determinations using whole (100 per cent) plasma. The mean prothrombin time of 813 determinations using diluted (12.5 per cent) plasma was 38.6 seconds with a standard deviation of 2.16 seconds (Table I). The ranges in seconds of the prothrombin time determinations were twelve to eighteen seconds and thirty-two to forty-two seconds for whole and diluted plasma, respectively.

TABLE I. NORMAL PROTHROMBIN TIMES

NO. OF DETERMINATIONS	PLASMA CONCENTRATION (PER CENT)	RANGE (SECONDS)	MEAN	STANDARD ERROR OF MEAN	STANDARD DEVIATION	STANDARD ERROR OF STANDARD DEVIATION
828	100.0	12–18	15.8	± .04	1.22	± .03
813	12.5	32–42	38.6	± .08	2.16	± .05

*Members of the staff of the Vascular Disease Research Laboratory and medical students who were 20 to 35 years of age.

Variations Between Individuals.—In order to study the variation between individuals a statistical analysis was made by the method of the analysis of variance of thirteen prothrombin readings on undiluted plasma from each of fifteen normal persons, a total of 195 prothrombin readings. The findings indicated that in these subjects the individual average prothrombin time, based on thirteen readings for each person, varied more from the general average for the total group than would have been expected from the amount of variation in prothrombin times for the same individuals when measured from their own individual averages. The differences from day to day in the prothrombin times of the same individual may be assumed to reflect a random combination of the results of daily changes in the individual under different conditions, plus the experimental error in the test itself under varying conditions in the same laboratory. On the other hand, the differences between the averages for different individuals of prothrombin readings taken under similar laboratory conditions is presumed to reflect the variability between individuals superimposed on that occurring in repeated tests of the same individual. For the persons thus studied, this variability between individuals was found to be greater than that for repeated prothrombin tests for the same individual so that the observed results could have been expected to happen on a chance basis considerably less than once in one hundred times.* The analysis of variance method similarly applied to the dilute (12.5 per cent) plasma readings for these same plasma samples and for these same individuals yielded similar results, although the level of significance was slightly lower. In this latter test it was found that the differences could occur on a chance basis between one and five times in one hundred.†

Likewise, inspection of the original data averaged for individuals supports the view that individuals differ in their average prothrombin times. Averages for these fifteen individuals based on thirteen readings each (numbers sufficient to stabilize major random fluctuations), actually varied by as much as two seconds for whole plasma readings and five seconds for diluted plasma readings. It would seem highly probable, therefore, that normal individuals do differ significantly from each other in their average prothrombin time. Final confirmation of this hypothesis would require further testing and statistical analysis. Furthermore, larger samples might make it possible to determine whether these variations between individuals were associated with other identifiable factors such as age, sex, and physical condition.

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*F = 2.53 for 14 degrees of freedom for the variance between persons and 180 degrees of freedom for the variance within persons.

†F = 2.06 for 14 degrees of freedom for the variance between persons and 180 degrees of freedom for the variance within persons.

F = variance ratio. It may be defined in general as the ratio of the square of the standard deviation of one distribution to the square of the standard deviation of another distribution. The square of the larger standard deviation is used as the numerator in computing this ratio and the level of its statistical significance is interpreted by means of an "*F*" table which takes into account the size of the two samples. In this instance the *F* test is used in conjunction with the method of the analysis of variance, and *F* means specifically the ratio resulting from dividing the square of the standard deviation of thirteen prothrombin readings each for fifteen normal individuals, each deviation being measured from the mean of the thirteen readings for the same individual, into the square of the standard deviation of the mean prothrombin times for each individual, the deviations in this instance being measured from the general mean prothrombin time for all sixteen subjects.

Variations Occurring During a Daily Cycle and Their Relation to the Intake of Unselected Food.—Blood samples for the prothrombin time determinations were taken from nine normal adults during a period of three weeks. One hundred prothrombin determinations were made on blood samples taken before breakfast, 109 on samples taken after breakfast, and 115 on samples taken after lunch (Table II). When the means and standard deviations of the prothrombin readings on samples taken before breakfast, on samples taken after breakfast, and on samples obtained after lunch are compared, respectively,* the differences are found to be slightly and somewhat inconsistent in direction. When treated for statistical significance, these differences were found to be significant at the 1.0 per cent level of confidence in some cases while in others they were definitely insignificant and probably of chance origin. The pattern in this respect also was inconsistent, suggesting that factors other than meal time or chance were operating to confuse the picture. If the intake of unselected food has any effect on prothrombin time, it is apparently of little importance.

TABLE II. SUMMARY OF THE ANALYSIS OF RELATION OF PROTHROMBIN TIME TO MEALS

NO. OF DETERMINATIONS	PLASMA CONCENTRATION (PER CENT)	RANGE (SECONDS)	MEAN	STANDARD ERROR OF MEAN	STANDARD DEVIATION	STANDARD ERROR OF STANDARD DEVIATION
828 Normal	100.0	12–18	15.82	± .04	1.22	± .03
100 Before breakfast	100.0	13–16	15.13	± .08	0.83	± .06
109 After breakfast	100.0	13–17	15.16	± .11	1.12	± .08
115 After lunch	100.0	12–17	14.61	± .12	1.24	± .08
813 Normal	12.5	32–42	38.59	± .08	2.16	± .05
100 Before breakfast	12.5	32–41	36.47	± .24	2.43	± .17
109 After breakfast	12.5	32–42	39.01	± .23	2.34	± .16
115 After lunch	12.5	33–42	38.16	± .18	1.96	± .13

Exercise.—The effect of exercise on prothrombin activity was studied in ten normal individuals. Blood samples were taken before and after the subject ran down and then up five flights of stairs, a total of 240 steps, or a distance of 145 feet. Thirty-four prothrombin determinations were performed before exer-

*Comparison with the general normal group was discarded as a procedure since the samples of the after breakfast group differed significantly from the samples of the general normal group also taken after breakfast.

cise. The mean was 17.09 seconds and 39.65 seconds using whole (100 per cent) and diluted (12.5 per cent) plasma, respectively. Immediately after exercise, thirty-four prothrombin determinations gave a mean of 17.03 seconds using whole (100 per cent) plasma and 39.6 seconds on diluted (12.5 per cent) plasma (Table III). The amount of exercise used in this test apparently had no measurable effect on the prothrombin level when tested under the conditions for this experiment since the very slight differences in the means and standard deviation of prothrombin readings taken before and after exercise were not statistically significant. In all probability they represent only chance variations. Since the same individuals were tested once before exercise and once again after exercise on the same day using the same laboratory methods and materials, uncontrolled factors were at a minimum. The purpose of this part of our study was to determine whether moderate exercise taken prior to having a prothrombin test performed might produce important variations in the result. No effort was made to study the effect of exercise to the point of complete exhaustion.

TABLE III. SUMMARY OF THE ANALYSIS OF THE RELATION OF EXERCISE TO THE PROTHROMBIN TIME

NO. OF DETERMINATIONS	PLASMA CONCENTRATION (PER CENT)	RANGE (SECONDS)	MEAN	STANDARD ERROR OF MEAN	STANDARD DEVIATION	STANDARD ERROR OF STANDARD DEVIATION
34 Before exercise	100.0	15–18	17.09	± .16	0.943	± .11
34 After exercise	100.0	15–18	17.03	± .14	0.882	± .11
34 Before exercise	12.5	36–42	39.65	± .23	1.33	± .16
34 After exercise	12.5	36–42	39.62	± .26	1.51	± .18

Cholesterol.—To ascertain whether the ingestion of a high-cholesterol diet affects the prothrombin activity, four normal subjects were given, in addition to their usual meals, six eggs a day and their plasma prothrombin times determined daily during a period of four weeks. The mean prothrombin times on sixty-six determinations using whole (100 per cent) plasma and diluted (12.5 per cent) plasma were 16.4 seconds and 39.1 seconds, respectively (Table IV). The means and standard deviations of these readings and the differences were found to be exceedingly small; in no case over 0.6 second. Only one of these differences was statistically significant at the 1.0 per cent level of confidence and one additional difference fell in the doubtful range between the 1.0 and 5.0 per cent level of significance. The two other differences were not statistically significant and may be considered chance variations. Probably the one difference termed statistically significant, even though slight, should not be attributed to the cholesterol diet since individuals normally vary slightly in their mean prothrombin levels and only four individuals were covered by this experiment.

TABLE IV. SUMMARY OF THE ANALYSIS OF THE RELATION OF HIGH-CHOLESTEROL DIET TO THE PROTHROMBIN TIME

NO. OF DETERMINATIONS	PLASMA CONCENTRATION (PER CENT)	RANGE (SECONDS)	MEAN	STANDARD ERROR OF MEAN	STANDARD DEVIATION	STANDARD ERROR OF STANDARD DEVIATION
828 Normal	100.0	12–18	15.8	± .04	1.22	± .03
66 High Cholesterol	100.0	14–18	16.4	± .15	1.19	± .10
813 Normal	12.5	32–42	38.59	± .08	2.16	± .05
66 High Cholesterol	12.5	32–42	39.05	± .33	2.62	± .23

SUMMARY AND CONCLUSIONS

1. The literature relating to the variations in tests for the prothrombin time, determined in individuals under different conditions, is confusing. Some of the inconsistency is undoubtedly due to differences in the technique used by the different authors. A method for performing a prothrombin test which has given reproducible results is presented in detail, namely, the Link-Shapiro modification of the Quick one-stage test.

2. Using this method, more than 800 determinations for whole plasma (100 per cent) and diluted plasma (12.5 per cent), respectively, were made on twenty-five normal subjects for periods of time from ten to forty weeks, and the following figures were obtained: for whole plasma, a mean value of 15.8 seconds ± 1.22; for dilute plasma, a mean value of 38.6 seconds ± 2.16. Studies for variations between different subjects indicated that individuals differ in their mean prothrombin times.

3. The variations occurring in the prothrombin times performed before and after breakfast and after lunch revealed that meals with random selection of foods do not affect the results of this test significantly.

4. Strenuous but not prolonged or exhausting exercise failed to produce significant changes in the prothrombin times.

5. The results of daily prothrombin studies in four subjects on a high-cholesterol diet for four weeks suggest that the major variations noted were not of an order to be clinically significant and were probably on some other basis.

6. Finally, we conclude that it is probably not necessary that blood for prothrombin tests be taken with the patient fasting and at bed rest.

The authors wish to acknowledge the valuable assistance of Miss M. E. Todd and Miss K. Taylor in this investigation and of Dr. D. F. Beck for the statistical analysis.

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THE EFFECT OF AMINOPHYLLINE ON THE PROTHROMBIN TIME OF NORMAL HUMAN PLASMA

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IT HAS been reported that the administration of methylxanthines to experimental animals shortens the prothrombin time of the plasma.[1,2] Similar observations on man were reported by Scherf and Schlachman.[3] However, several investigators have failed to obtain similar results in animal or human experiments.[4-12] Because of this controversy and the clinical importance of the drugs, it was thought advisable to reinvestigate the problem. The apparent discrepancy may lie in the uncertainties of methods for assay of prothrombin times or in factors as yet unknown.

METHOD

Fifteen normal adults of both sexes, ranging from 25 to 35 years of age, were used in this experiment. The prothrombin times were determined by the Link-Shapiro[13,14] modification of the Quick[17] one-stage method. The method as routinely used in our laboratory has been previously described.[15] Prothrombin time determinations were also done by the method of Fullerton,[16] using Russell Viper Venom as thromboplastic agent, and by the method of Quick,[17] using rabbit-lung thromboplastin instead of rabbit-brain thromboplastin. Daily prothrombin time determinations were done when possible on whole (100 per cent) plasma and diluted (12.5 per cent) plasma. All tests were performed on blood samples taken in the morning and were completed within two hours after the specimens were drawn. Each individual was subjected to the following routine. Two or three control prothrombin determinations were made. Aminophylline was then administered orally in doses of 200 mg. three times a day or 600 mg. daily for a total of fourteen days. The dosage of aminophylline was then increased to 1.0 Gm. per day for four weeks.

DISCUSSION

The results of the study as obtained by the three methods of determining the prothrombin time are summarized in Tables I, II, and III. It is doubtful

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TABLE I. SUMMARY OF ANALYSIS OF EFFECT OF AMINOPHYLLINE ON PROTHROMBIN TIME AS DETERMINED BY THE LINK-SHAPIRO MODIFICATION OF ONE-STAGE PROTHROMBIN DETERMINATION

AMOUNT OF AMINOPHYLLINE ADMINISTERED DAILY	NUMBER OF DETERMINATIONS	PLASMA CONCENTRATION (PER CENT)	RANGE (SECONDS)	MEAN	STANDARD ERROR OF MEAN	STANDARD DEVIATION	STANDARD ERROR OF STANDARD DEVIATION
None	36	100.0	13–18	15.56	±.25	1.47	±.17
None	36	12.5	35–45	40.08	±.45	2.64	±.31
600 mg.	60	100.0	13–19	16.68	±.18	1.42	±.13
600 mg.	59	12.5	34–45	39.91	±.30	2.25	±.21
1.0 Gm.	151	100.0	12–20	16.17	±.11	1.35	±.08
1.0 Gm.	151	12.5	32–45	39.20	±.21	2.58	±.15
None	828*	100.0	12–18	15.8	±.04	1.22	±.03
None	813*	12.5	32–42	38.6	±.08	2.16	±.05

*Reference 15.

TABLE II. SUMMARY OF ANALYSIS OF EFFECT OF AMINOPHYLLINE ON PROTHROMBIN TIME AS DETERMINED BY QUICK METHOD USING RABBIT LUNG THROMBOPLASTIN INSTEAD OF RABBIT-BRAIN THROMBOPLASTIN

AMOUNT OF AMINOPHYLLINE ADMINISTERED DAILY	NUMBER OF DETERMINATIONS	PLASMA CONCENTRATION (PER CENT)	RANGE (SECONDS)	MEAN	STANDARD ERROR OF MEAN	STANDARD DEVIATION	STANDARD ERROR OF STANDARD DEVIATION
None	25	100.0	13–19	16.26	±.34	1.66	±.23
None	25	12.5	39–45	42.38	±.41	1.99	±.28
600 mg.	32	100.0	13–22	17.0	±.36	2.02	±.25
600 mg.	32	12.5	34–50	41.0	±.56	3.10	±.39
1.0 Gm.	90	100.0	12–21	17.1	±.19	1.80	±.13
1.0 Gm.	90	12.5	30–46	40.7	±.35	3.29	±.25

whether the slight differences in the means indicate that aminophylline, even in large doses, has an effect on the prothrombin time of supposedly normal adults. All the means fall well within the range usually found for single readings from normal individuals not receiving aminophylline. The prothrombin times on two individuals receiving 1.8 Gm. of aminophylline for one day were well within the normal range. However, because of the toxicity of aminophylline at this dosage level, the drug was discontinued.

TABLE III. SUMMARY OF ANALYSIS OF EFFECT OF AMINOPHYLLINE ON PROTHROMBIN TIME AS DETERMINED BY THE FULLERTON METHOD USING RUSSELL VIPER VENOM AS THROMBOPLASTIN AGENT

AMOUNT OF AMINOPHYLLINE ADMINISTERED DAILY	NUMBER OF DETERMINATIONS	PLASMA CONCENTRATION (PER CENT)	RANGE (SECONDS)	MEAN	STANDARD ERROR OF MEAN	STANDARD DEVIATION	STANDARD ERROR OF STANDARD DEVIATION
None	22	100.0	12–20	17.1	±.45	2.06	±.31
None	22	12.5	34–42	39.5	±.45	2.08	±.31
600 mg.	16	100.0	14–24	18.8	±.65	2.52	±.45
600 mg.	16	12.5	38–53	43.06	±.85	3.30	±.59
1.0 Gm.	49	100.0	12–22	18.38	±.43	2.98	±.30
1.0 Gm.	49	12.5	35–46	41.07	±.41	2.81	±.28

CONCLUSION

The results of these studies appear to indicate that the oral administration of clinical doses of aminophylline to normal adults has no effect on the prothrombin time determination and probably is of no clinical significance.

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THE EFFECT OF ERGOTAMINE TARTRATE ON THE ABNORMAL ELECTROCARDIOGRAM IN PATIENTS PREVIOUSLY PREPARED WITH TETRAETHYLAMMONIUM CHLORIDE

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THE changes in the T waves which may occur with a change in posture, have been thought by some authors to be due to a change in sympathetic tone. Nordenfeldt,[7] in a series of experiments, demonstrated that the injection of ergotamine tartrate would prevent the recurrence of posturally inverted T waves in patients who previously had shown such changes with the assumption of the erect posture. Wendkos[11] stated that inverted T waves which may occur in the emotionally tense person or the neurocirculatory asthenic may be prevented or normalized by the use of a sympathicolytic drug. He also concluded that excessive sympathetic tone was responsible for the inverted T waves and that, with the use of ergotamine tartrate, a differentiation between functionally inverted and organically inverted T waves could be made.

In a previous series of experiments[9] it was found that the positional inversion of previously upright T waves was not always prevented with the use of ergotamine tartrate and it was demonstrated also that normalization of inverted T waves due to organic heart disease could be induced by the administration of ergotamine preparations.[10]

Because these results were not consistent with those of the previous investigators, it was thought that the normalization of inverted T waves by ergotamine was not due to changes in sympathetic tone. The appearance of anginal pain after the injection of ergotamine preparations and the normalizing of organically inverted T waves suggested a direct action of these preparations either on the coronary arteries or on the heart muscle.

The development and clinical application of tetraethylammonium chloride introduced a means of blocking the transmission of impulses across the autonomic ganglia so that the direct action of ergotamine tartrate on the heart muscle or coronary arteries could be studied. During these experiments, some coincidental observations were made on the effect of tetraethylammonium chloride on the blood pressure and on the electrocardiogram.

METHOD OF STUDY AND MATERIAL

All patients studied had a sustained and marked hypertension and their control electrocardiogram showed the pattern of left ventricular strain with a depression of the RS-T segment and an inversion of the T waves in Lead I and the chest lead with the exploring electrode over the left ventricle (CF_5). All experiments were done with the patients in the supine position. Control electrocardiograms and blood pressure recordings were taken. The patients were then

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given an intravenous injection of 100 to 300 mg. tetraethylammonium chloride,* and the electrocardiogram and blood pressure were retaken within two minutes after the injection. The blood pressure was taken thereafter at two-minute intervals and the electrocardiogram at irregular periods, depending upon the fluctuations in the blood pressure. In some patients, the effect of TEA on the blood pressure and electrocardiogram was followed for forty minutes, while in others an intravenous injection of ergotamine tartrate† was given three to ten minutes after the TEA injection.

Electrocardiograms and blood pressure recordings were made five, fifteen, and thirty minutes following the injection of ergotamine tartrate. The criterion for effective ganglia blockade in these experiments was the precipitous fall and maintenance of blood pressure at a level significantly lower than the control reading.

RESULTS

Sixteen patients, whose ages ranged from 50 to 81 years, were studied. All of them received TEA, and, in addition, ten were given ergotamine tartrate. One patient showed normalization of the inverted T waves in Leads I and CF_5 on two different occasions with TEA alone. Six of the ten patients who received ergotamine tartrate in addition to the TEA developed normalization of the organically inverted T waves. This normalization occurred in either Leads I or CF_5 or in both leads.

Figure 1,*A* is the control electrocardiogram of a 63-year-old man who was in advanced left- and right-sided heart failure. The control blood pressure was 240/110. The electrocardiogram shows an inversion of the T waves in Leads I, II, and CF_5 with a depression of the RS-T segments. Figure 1,*B* was recorded two minutes after the intravenous injection of 200 mg. of tetraethylammonium chloride. The blood pressure had fallen to 160/70, but no significant changes occurred in the electrocardiogram. Five minutes after the injection the blood pressure was 155/85, and at ten minutes 170/95 (Fig. 1,*C*). Fifteen minutes after the injection the blood pressure was 195/100, and at twenty-five minutes 205/105 (Fig. 1,*D*). The electrocardiograms taken at these periods remained unchanged.

Figure 2,*A* is the control electrocardiogram of the same patient taken on the following day. The control blood pressure was 240/100. Figure 2,*B* was taken two minutes after the injection of 200 mg. of TEA and is similar to the control. At this time the blood pressure had fallen to 175/75. Figure 2,*C* was taken five minutes after the injection of TEA and two minutes after an intravenous injection of 0.5 mg. ergotamine tartrate. At this time, the blood pressure had risen to 280/120 and the electrocardiogram shows a sinus tachycardia and a definite decrease in the inversion of the T waves in Leads I and CF_5. Figure 2,*D*, taken fourteen minutes after TEA and ten minutes after ergotamine tartrate, shows upright T waves in Lead CF_5, and the blood pressure was 240/100. Twenty-four minutes after TEA and twenty minutes after ergotamine tartrate (Fig. 2,*E*) the

*Tetraethylammonium chloride will be referred to as TEA in this paper. We are obliged to Mr. W. L. Schreier, of Parke, Davis & Co., for the supply of tetraethylammonium chloride (Etamon chloride) used in this investigation.

†Ergotamine tartrate will be designated as E.T. in the demonstrating figures.

electrocardiogram shows that the T waves are still upright in Lead CF_5. The blood pressure was 225/115. The patient complained of precordial pain ten minutes after the injection of ergotamine tartrate which still persisted when the experiment was terminated thirty minutes after the injection of ergotamine tartrate.

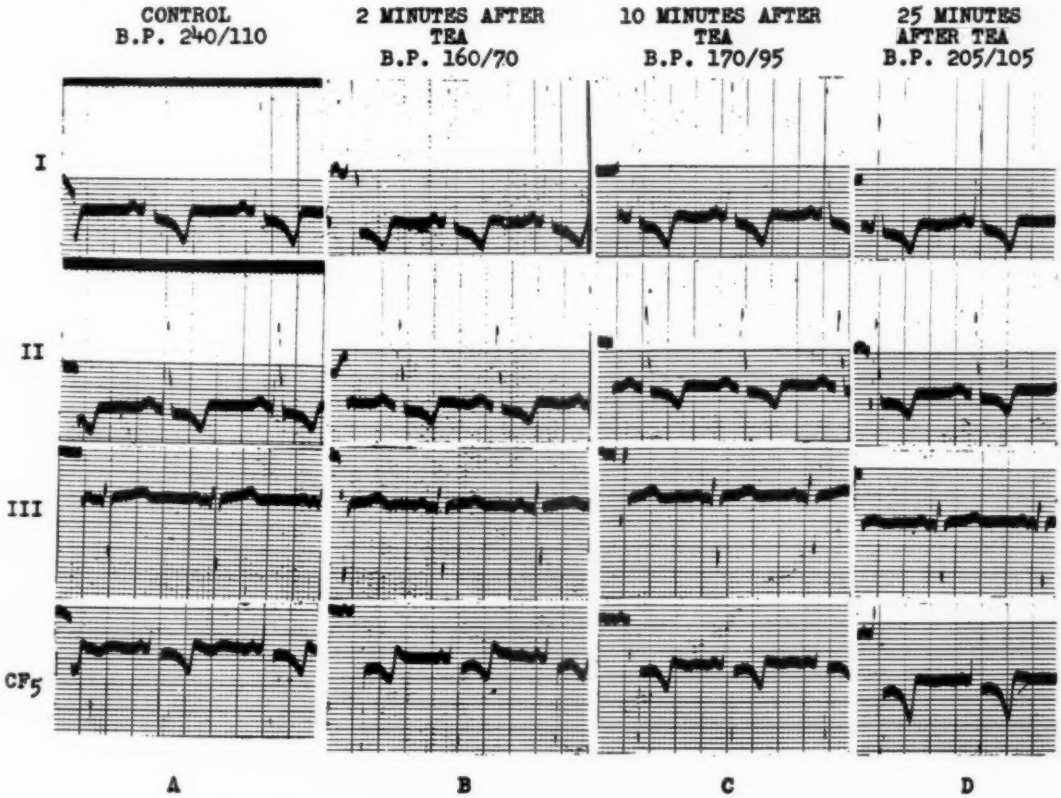

Fig. 1.—*A* shows the pattern of left ventricular strain with a control blood pressure of 240/110. Two minutes after the injection of TEA (*B*) the blood pressure had fallen to 160/70 with no change from the control electrocardiographic pattern. The electrocardiogram does not change ten (*B*) and twenty-five minutes (*C*) after the injection of tetraethylammonium chloride.

Figure 3 graphically depicts the blood pressure changes and simultaneous electrocardiographic tracings of the patient whose findings are demonstrated in Figs. 1 and 2. When TEA alone was given (Fig. 3,*A*), no significant electrocardiographic changes occurred with either the fall or rise of the blood pressure. When, however, ergotamine tartrate was injected, in addition to the TEA, an immediate and profound rise occurred in the blood pressure (Fig. 3,*B*). Significant electrocardiographic changes took place ten minutes after the injection of ergotamine tartrate.

Figure 4,*A* is the control electrocardiogram of a 68-year-old hemiplegic man with a hypertension of 220/140. This shows inverted T waves in Leads I and CF_5, a pattern commonly seen in left ventricular hypertrophy. Two minutes

after the injection of 300 mg. of TEA, the blood pressure fell to 120/100 and the T waves in Leads I and CF_5 became upright while those in Lead II were much taller (Fig. 4,*B*). There is no appreciable change in heart rate after the injection of tetraethylammonium chloride. This same patient had received 300 mg. of TEA on the previous day and within two minutes of the injection also showed

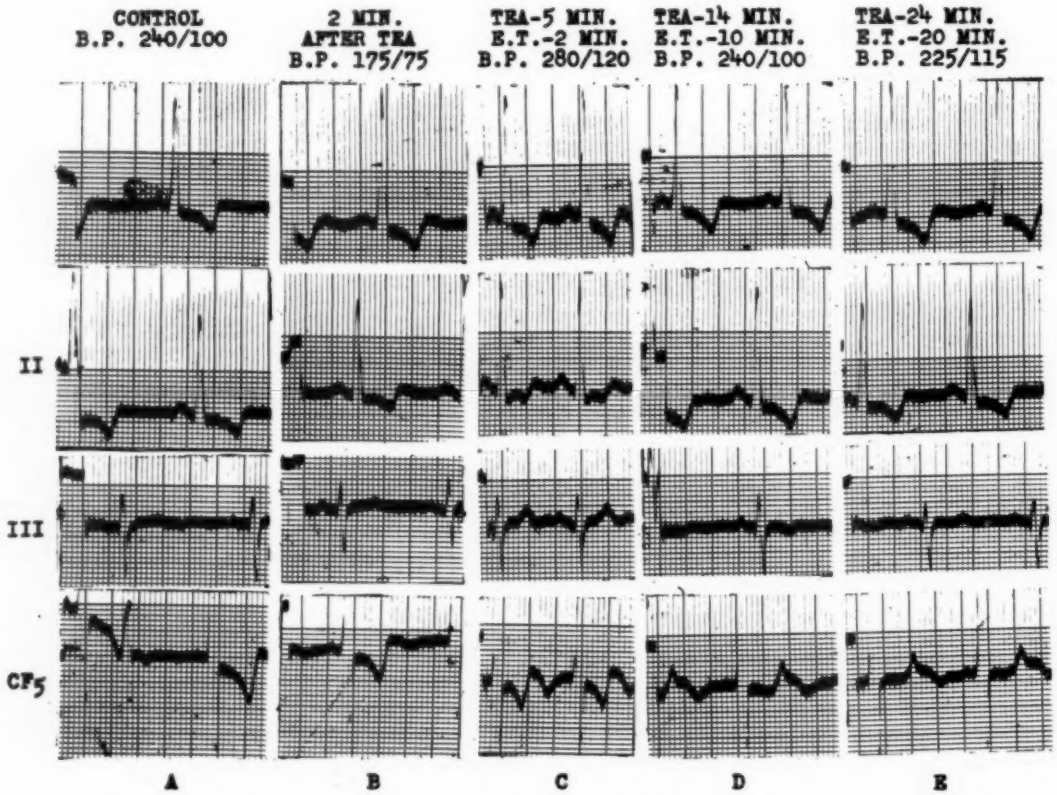

Fig. 2.—*A* is the control electrocardiogram taken on the same patient on the following day. *B*, taken two minutes after the injection of TEA and during the fall in blood pressure, reveals no electrocardiographic changes. Two minutes after the additional injection of ergotamine tartrate (*C*) the blood pressure had risen to 270/120 but the electrocardiogram was unchanged. *D* and *E* show the normalization of the T waves in Lead CF_5 ten and twenty minutes respectively after the injection of ergotamine tartrate.

normalization of the T waves in Leads I and CF_5 with a drop of blood pressure to 110/80. However, at that time the normal sinus rhythm was replaced by an A-V nodal one, with the P waves buried in the QRS complexes (Fig. 5,*A*). Within five minutes the electro-cardiogram had returned to its control picture and the blood pressure had risen to 145/100. In the present experiment, however, the normal sinus rhythm persisted. Nine minutes after the injection of TEA and five minutes after the additional injection of ergotamine tartrate (Fig. 4,*C*) the blood pressure had risen to 190/125 and the electrocardiogram had returned to the control picture. Thirty-four minutes after the injection of TEA and thirty minutes after the injection of

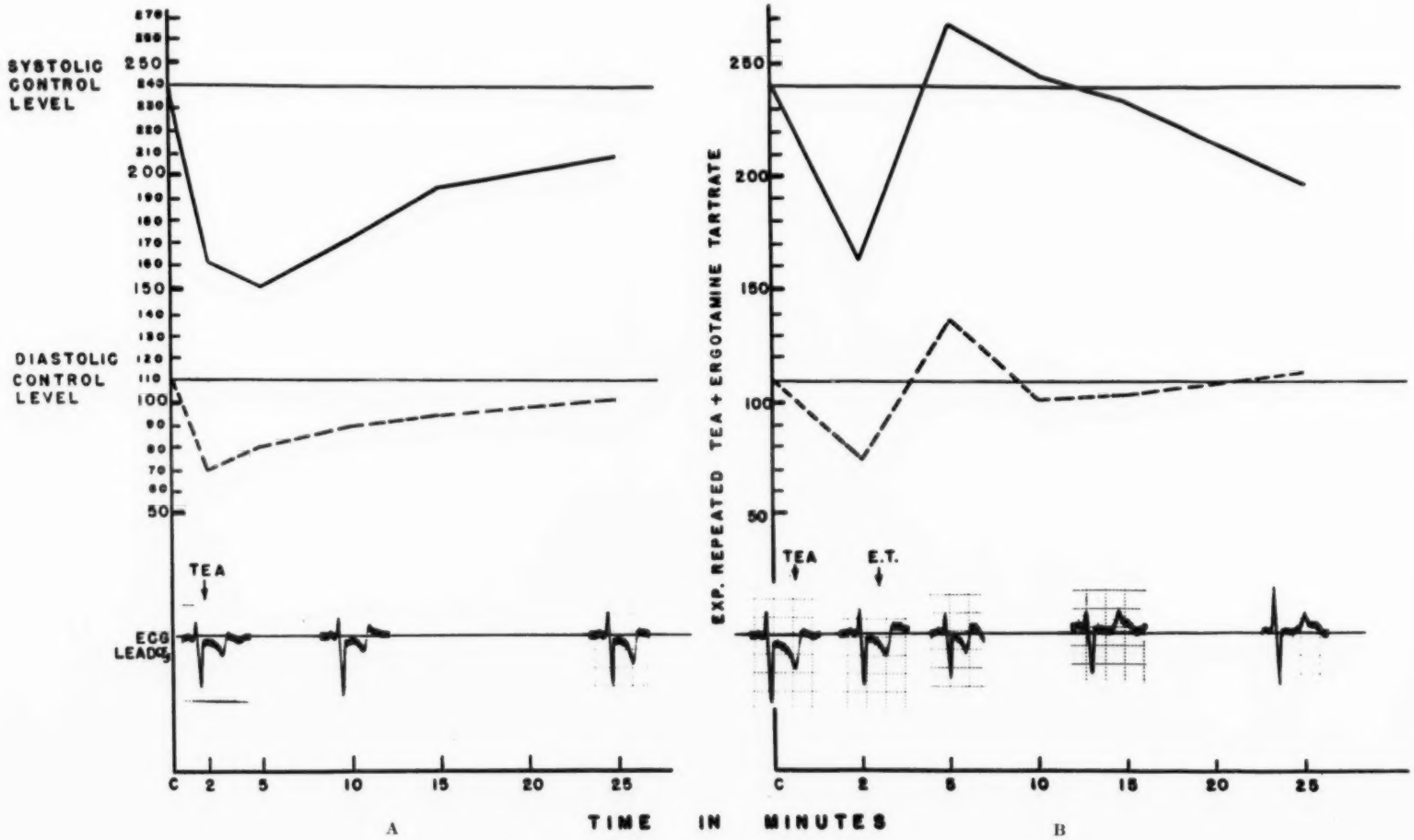

Fig. 3.—Graphic representation of the events as described in Figs. 1 and 2. *A* depicts the changes after the injection of TEA alone; *B*, after the injection of TEA and the additional injection of ergotamine tartrate.

ergotamine tartrate the blood pressure was 225/120 and the electrocardiogram resembled those depicted in Figs. 4,*A* and 4,*C*.

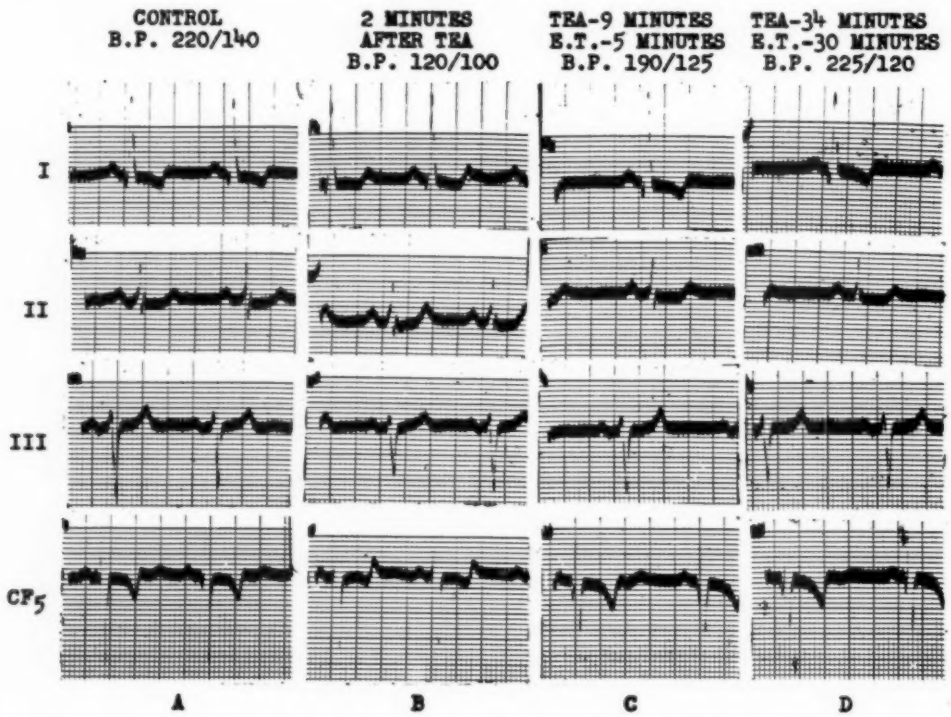

Fig. 4.—In *B*, two minutes after the injection of TEA the blood pressure fell from 220/140 to 120/100 and normalization of the T waves has occurred in Leads I and CF_5. In *C*, nine minutes after the injection of TEA and five minutes after the additional injection of ergotamine tartrate, the electrocardiogram has returned to the pattern of a left ventricular strain and the blood pressure has risen to 190/125. In *D* this pattern persists but the blood pressure is now 225/120.

Figure 5 is a graphic representation of the events in the experiments on this patient as they occurred on the two successive days.

DISCUSSION

TEA caused an immediate and profound fall in blood pressure in all of the patients studied and this fall persisted up to forty minutes in some patients, while in others the blood pressure began to rise within ten to fifteen minutes, but did not reach the control level for some time. Only one patient showed significant electrocardiographic alterations. In one patient the blood pressure fell to an unobtainable level, and a Jacksonian fit occurred, with a loss of consciousness which lasted for three minutes. In spite of the very low blood pressure, no electrocardiographic changes were demonstrated. Therefore, one may conclude that the blocking of the autonomic ganglia and the fall of the blood pressure are not alone responsible for the electrocardiographic alterations.

The addition of ergotamine tartrate caused an immediate and profound rise in blood pressure which at times reached levels far above the control readings

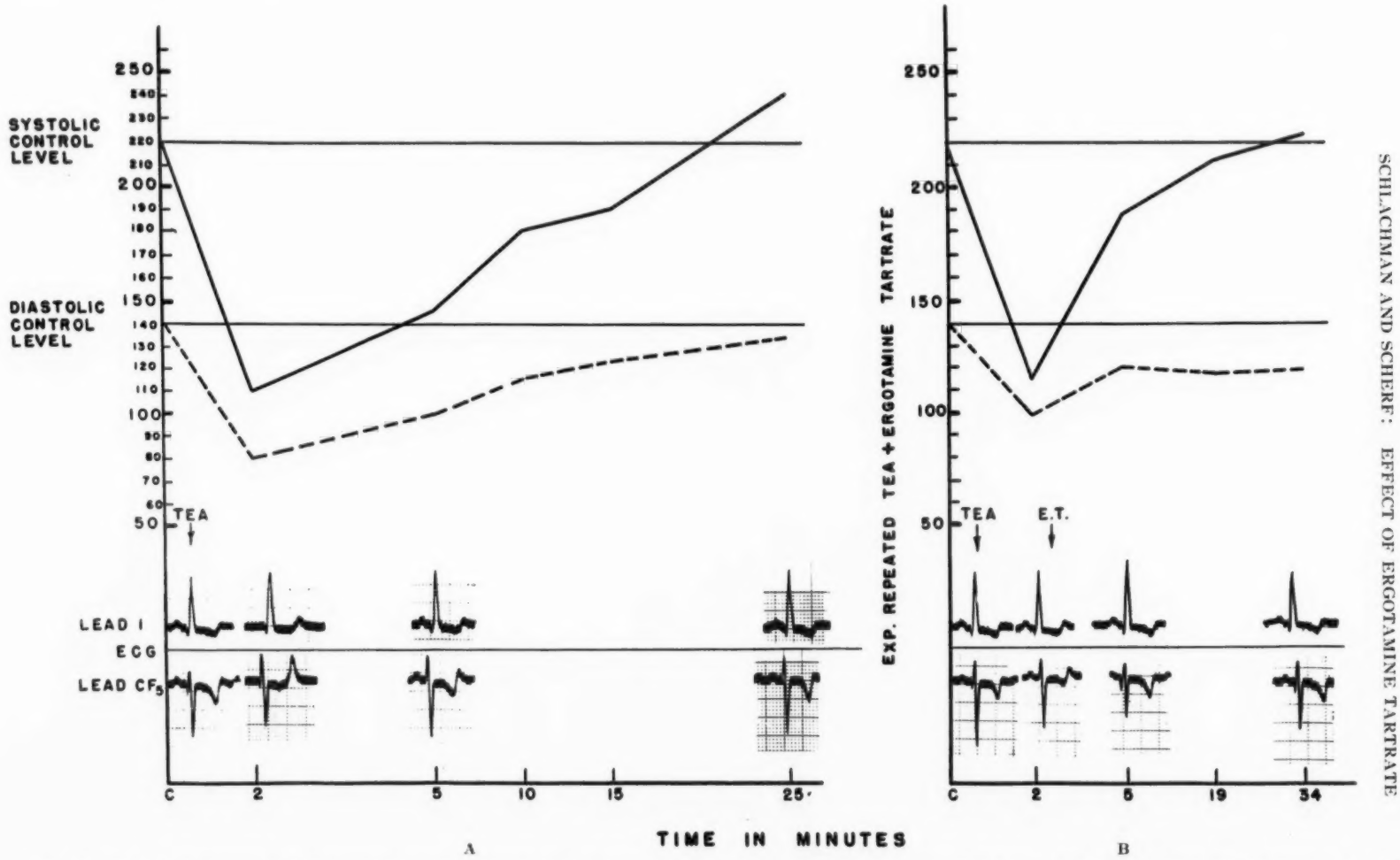

Fig. 5.—The blood pressure and electrocardiographic changes as they occurred in the same patient on two successive days. *A* shows the effect of TEA alone and *B* the effects of TEA and the additional injection of ergotamine tartrate. Normalization of the T waves occurred on both days after the injection of tetraethylammonium chloride. In *A*, however, an A-V nodal rhythm accompanied the normalization of the T waves within two minutes after the injection of TEA while in *B* normal sinus rhythm persisted. The addition of ergotamine tartrate caused an immediate rise in blood pressure but no electrocardiographic changes.

This rise was most pronounced in those patients who had a preliminary autonomic ganglia blockade with tetraethylammonium chloride. It is to be emphasized that the action of ergotamine tartrate occurred while the patient's nervous system was still under the influence of tetraethylammonium chloride. The normalization of the T waves began within five minutes after the injection of ergotamine tartrate in many patients and was complete within fifteen minutes. Although the rise of blood pressure is immediate, there is a lag in the beginning of the electrocardiographic changes.

This sudden and rapid rise in blood pressure after the administration of ergotamine tartrate demonstrates the peripheral vasoconstricting property of the drug. Bluntschli and Goetz[3] have found that ergotamine tartrate causes a greater vasoconstriction when a preliminary vasodilatation has been produced. In their experiments, a local vasodilatation of one extremity was produced by a surgical preganglionic sympathectomy and they found that vasoconstriction was greater after the injection of ergotamine tartrate in the sympathectomized than in the unsympathectomized limb. In previous experiments with ergotamine tartrate[10] without the preliminary use of TEA, we also demonstrated a rise in blood pressure, but it did not approach the levels obtained in this present series.

It has been shown that the action of the sympathicolytic component of ergotamine tartrate is abolished by preganglionic sympathectomy and the conclusion is that this action is not on the sympathetic myoneural junction, but on the higher centers.[3]

In a previous study it was shown that normalization of organically inverted T waves could be produced by ergotamine tartrate without first preparing the patient with tetraethylammonium chloride.[10] Therefore, whether a sympathetic paralysis exists or not, ergotamine tartrate will invoke similar changes on organically inverted T waves. This would indicate a vasoconstricting action of ergotamine tartrate on the coronary arteries and the frequent occurrence of anginal pain following the administration of ergotamine preparations would also indicate the presence of coronary vasoconstriction.

The action of ergotamine in causing normalization of organically and functionally inverted T waves is not due, as Nordenfelt[7] and Wendkos[11] have contended, to its sympathicolytic action but is due to its local action on the coronary arteries or on the myocardium.

The most probable explanation for the electrocardiographic changes produced by ergotamine tartrate is a change in the repolarization process which in turn causes an alteration of the ventricular gradient.[2]

It has been shown experimentally in animals and it has been proved in man that acute hemorrhage may lead to damage of the subendocardial layers of the myocardium. Acute hemorrhage in patients with a left ventricular strain pattern may cause a normalization of the T waves in Leads I, II, and in the chest leads over the left ventricle,[8] a change similar to that induced by the injection of ergotamine tartrate.

The normalization by TEA of the inverted T waves which occurred on two occasions in the same patient must also be due to a change in the repolarization process produced by the coronary artery dilatation and improved coronary cir-

culation. In spite of the profound drop in blood pressure, following the injection of TEA, it has been shown that the cardiac output increases by 20 per cent and the peripheral blood flow is also increased as indicated by a rise in skin temperature.[6]

In several patients, the pain associated with myocardial infarction was relieved by TEA,[6] a pain whose genesis is that of myocardial ischemia. It is, therefore, not amiss to assume that the coronary arteries also participate in the generalized vasodilatation induced by tetraethylammonium chloride.

Thus it is possible for two opposite coronary artery actions, such as coronary vasoconstriction by ergotamine tartrate and coronary vasodilatation by TEA, to cause a change in the repolarization process.

The great fall in blood pressure produced by TEA in this group of patients with sclerosis of the peripheral arteries indicates that a sympathetic vasoconstriction still plays an important role in the maintenance of an elevated blood pressure in this older age group. Tetraethylammonium chloride will not cause a drop in blood pressure in the absence of vasoconstrictor tone.[6]

Lyons and his associates[6] in a study of 143 hypertensive patients, in the younger age group, found that the average fall in systolic blood pressure was 23.5 mm. Hg and the diastolic drop was 19.3 millimeters. This group of older patients studied by us showed an average fall in systolic blood pressure of 81.3 mm. Hg and a diastolic drop of 30.0 millimeters. Other authors have found also a greater hypotensive response in the older hypertensive subject.[4,6] This would indicate that, in spite of advanced arteriosclerosis and so-called fixed hypertension, TEA can produce vasodilatation in the older patient.

Little is known about the electrocardiographic changes caused by tetraethylammonium chloride. Hayward[5] found that at the lowest level of the blood pressure fall after the administration of TEA the electrocardiogram showed no change other than an increase in heart rate. The ventricular complexes whether they were normal or abnormal before the administration of TEA remained unchanged. Acheson and Moe[1] found that TEA in dogs in doses far exceeding those used in the human being will produce an increase in the height of the T waves in the same direction as the P waves. This change occurs usually in Lead I. The RS-T segment slopes, being no longer isoelectric, and the electrocardiogram returns to normal within two to six minutes. Larger doses may give rise to ventricular extrasystoles singly or in groups, A-V nodal rhythm, and ventricular tachycardia and even larger doses, ventricular fibrillation.

In spite of the fact that all of the patients studied had advanced circulatory changes and all had electrocardiographic alterations indicative of organic heart disease and many of them were in cardiac decompensation, TEA did not cause any toxic reactions which would be considered alarming except in one patient. This disconcerting reaction was the loss of consciousness associated with a Jacksonian fit due to a fall in blood pressure to zero. This attack lasted but three minutes and the patient was back to his original state after that time although the blood pressure remained at a low level for forty-five minutes. Other investigators have found that TEA will relieve the dyspnea and orthopnea of hypertensive heart failure.[4,5] It would seem that TEA is a safe preparation.

The marked changes that drug administration may produce in the abnormal electrocardiogram with the pattern of left ventricular strain, independent of the height of the blood pressure, are of clinical significance. Furthermore, such observations should make one cautious in the interpretation of T-wave alterations and the diagnosis of progression or regression of a myocardial disease from such wave changes alone.

CONCLUSIONS

1. The normalization of organically inverted T waves, as seen in left ventricular hypertrophy, by ergotamine tartrate is due to its vasoconstricting action on the coronary arteries and not to its sympathicolytic component.

2. The preliminary preparation of the patient with TEA, which causes an autonomic ganglia blockade, does not alter the normalization of these inverted T waves by ergotamine tartrate and this normalization may be seen whether or not there is a preliminary blockade with tetraethylammonium chloride.

3. The preliminary preparation of the patient with tetraethylammonium chloride enhances the vasoconstricting properties of ergotamine tartrate as indicated by the immediate and profound rise in blood pressure after its injection and completely eliminates the sympathicolytic component of ergotamine tartrate.

4. The probable cause for the normalization of the T waves is a change in the repolarization of the myocardium induced by the coronary vasoconstricting property of ergotamine tartrate and rarely by the vasodilating ability of tetraethylammonium chloride.

5. Tetraethylammonium chloride causes a greater fall in blood pressure in the older than in the younger hypertensive patient and is a safe drug to use even in patients with cardiovascular disease.

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HEMORRHAGE INTO THE ARTERIAL WALL AS A CAUSE OF PERIPHERAL VASCULAR DISEASE

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IT HAS been known for a long time that bleeding frequently occurs in the intima of a sclerotic artery, but the importance of such intimal hemorrhage as a precipitating factor in arterial thrombosis has only recently been pointed out. Morgagni[1] described "a large kind of ecchymosis" in a case of dissecting aneurysm of the aorta and since that time, and perhaps even before it, pathologists have noticed hematomas and mural thrombi in atheromatous plaques in the aorta and other arteries of the body. For many years it was thought that these hemorrhages were the result of breaks in the integrity of the intima which permitted infiltration of blood from the main current into the coats of the diseased artery. It is now well established, however, that in most cases these hemorrhages are the result of rupture of the capillaries ramifying within the diseased intima or media, and arising either from the lumen of the sclerotic artery or the vasa vasorum. In health the vasa vasorum penetrate to the media of large arteries, but do not enter the intima. In disease, however, and especially in arteriosclerosis, vasa vasorum are present in the thickened intima. This observation was made as long ago as 1876 by Köster,[2] who also drew attention to the relation between the vasa vasorum and the localization of arterial disease. This view has been corroborated by the work of Robertson.[4] In 1936, Paterson[5] again drew attention to the intimal vascularization which frequently occurs in coronary thrombosis and is accompanied by varying degrees of hemorrhage. He produced convincing evidence that "vascularization of the intima of coronary arteries by discrete capillaries which arise from their lumens was a common finding in association with atherosclerosis." He found that vascularization, while particularly marked in thrombosed coronary arteries, was not present in normal coronary arteries. Because of the finding of intimal capillaries, plaques of atheromatous material, capillary rupture, and hemorrhage in all his cases of recent thrombosis, Paterson suggested that these factors might lead to thrombosis.

In 1937 Wartman[6] published a preliminary report in which he verified Paterson's findings and described six cases of sclerotic arteries which were occluded not by thrombi, but by large intimal hematomas. Later, in 1938, he pointed out that such hemorrhages, whether large or small, might rupture and lead to thrombus formation.[7] As was to be expected small hematomas in the intima were also found which caused neither stenosis nor thrombosis.[8] In 1938, Paterson[9] independently described similar lesions. Since then the work of these authors

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has been repeatedly verified.[10-14] As a result of these and other studies it is now well established that intimal vascularization and bleeding are important phenomena of arteriosclerosis no matter where it occurs and that this bleeding is frequently a precipitating factor in thrombosis.

Not only does intramural hemorrhage occur in the coronary arteries, but it has been observed in most of the large arteries of the body. Intimal vascularization and hemorrhage have been described in the pulmonary[8,15] and cerebral[3,16] arteries where they are often associated with cerebral thrombosis. They have also been observed in the carotid and renal arteries[8] and in most of the branches of the aorta including the femoral arteries.[10]

The purpose of this article is to call attention to the fact that intramural hematomas occur in the arteries of the lower extremities and may cause occlusion either by pressure alone or by rupture and subsequent thrombus formation. No doubt the lesion is often overlooked because the limitations imposed on most autopsies preclude examination of the femoral and iliac arteries. Since this is true in this series also no attempt has been made to estimate statistically the incidence of intimal vascularization and hemorrhage in the arteries of the leg. Instead three cases will be reported in which hemorrhage into the intima or media was a precipitating factor in the obstruction.

MATERIAL AND METHODS

The material was obtained from autopsies performed on three adults. The affected parts of the arteries were removed completely, washed free of blood with tap water, and fixed in 10 per cent neutral formalin. The specimens were then cleared by the Spalteholz method. Step blocks were taken of the occluded portions as well as of other areas of interest and embedded in paraffin. Often semiserial sections were cut in order to study certain lesions in their entirety. The sections were stained with hematoxylin and eosin, Masson's trichrome stain, and a combination of van Gieson's and Weigert's elastica stains. Perle's stain for iron was used for the demonstration of iron pigment.

CASE REPORTS

CASE 1.—W. S. C., a white man, 57 years of age, said that during the previous two years he had suffered from aching and cramping pains in his left calf which appeared after he walked a short distance and were relieved by rest. Two weeks before admission to the hospital he noticed a small ulcer midway down the left calf which drained a small amount of pus. A tender spot had been present on his left heel for about the same length of time. The patient was known to have had hypertension for twelve years.

The blood pressure on admission was 170/100. The left foot was pale, with cyanosis of the toenail beds, and was colder than the right, becoming pallid on elevation and red on suspension. A small ulcer, 2.5 cm. in diameter, was present on the left calf and was covered with a scab. There was a roughly triangular area of dusky cyanosis on the left heel which was extremely tender and was ulcerated on the outer aspect. The dorsalis pedis and posterior tibial arteries on the left foot were not palpable. The dorsalis pedis on the right side was faintly palpable, but the posterior tibial artery was imperceptible. No pulsation was felt in either popliteal space, although there were faint pulsations over both femoral rings. The usual laboratory examinations gave negative results. Electrocardiograms showed no abnormality. X-ray examination of the heart showed mild enlargement of the left ventricle and atrium, and slight dilatation and tortuosity of the aorta. No calcified vessels could be demonstrated in the feet and lower legs. All the bones of the legs were osteoporotic.

Each day the patient was given 5 per cent sodium chloride intravenously and intermittent vascular occlusion, but with no resulting change in his condition. On the morning of the forty-second hospital day he appeared in his usual health until about 10:30 A.M. when he complained of slight abdominal distress and nausea. A few moments later he died.

At autopsy the heart weighed 525 grams and was moderately dilated. It showed marked fibrosis and both fat infiltration and fatty degeneration of the myocardium. The kidneys were the seat of moderate arterial and arteriolar sclerosis. No cause for the sudden death was found.

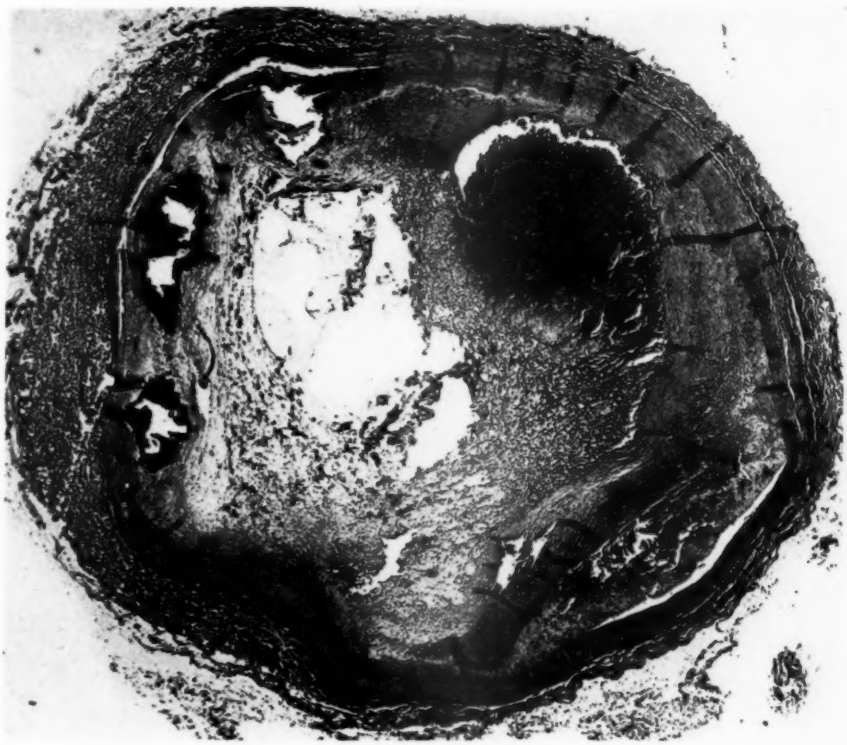

Fig. 1.—Case 1. Section from left common iliac artery. Several hemorrhages are present in the arteriosclerotic intima. The large one at the top of the picture has ruptured and is continuous with the thrombus. (Hematoxylin and eosin stain, ×20.)

The aorta was the seat of profound arteriosclerosis which was most marked in the abdominal portion. Immediately below the renal arteries a friable, mottled yellow and red thrombus, which was firmly adherent to the intima, occluded the lumen and extended to the bifurcation of the aorta. In the cleared specimen the rich vascularization of the intima and the numerous small hemorrhages in the neighborhood of the thrombus were easily seen. At one point, approximately 2 cm. above the bifurcation, a very large hematoma had ruptured and an occluding thrombus had formed at the site of rupture.

The left common iliac artery was occluded beginning at a point 2 cm. from the bifurcation of the aorta and extending distally for a distance of 4 centimeters. The occlusion was caused by a firm, slightly retracted, pale reddish-gray thrombus for the first centimeter. Distal to this area the clot was dark red for a distance of 2 cm., after which it was again pale gray.

The first portion of the right common iliac artery was occluded by a fresh thrombus, similar to that seen in the aorta. Intramural hematomas were easily demonstrated in the cleared specimen and several of them communicated with the thrombus.

Sections were cut from the aorta midway beeween the renal artery, and the bifurcation. These showed far-advanced arteriosclerosis with great thickening of the intima by atheromatous plaques which were remarkable because of extensive vascularization at the periphery of the lesions. For the most part the vessels in the vascularized areas were dilated capillaries which were often surrounded by a small zone of extravasated red blood cells. These vessels arose either from the main arterial lumen, the vasa vasorum, or from the branch arteries of the aorta. In one section there was a large intimal hematoma which had ruptured, and, since both the hematoma and the thrombus were composed of laked and hemolyzed red blood cells, a little fibrin, and a few leucocytes, but showed no evidence of organization, they were thought to be of the same age.

The media also showed vascularization, although not to as marked a degree as the intima. The adventitia showed small foci of lymphocytes, especially around the vasa vasorum, which themselves were often the seat of extensive arteriosclerosis with marked intimal hyalinization but without occlusion or serious stenosis of the lumens.

Sections of both common iliac arteries showed lesions which were practically identical with those in the aorta (Fig. 1). They were the seat of extensive arteriosclerosis and there were several large hematomas in the wall of the intima, one of which was ruptured. It was again noted that the hematomas and the thrombus appeared of the same age, neither showing evidences of organization, which suggested that rupture of the intimal hematoma led to thrombosis.

CASE 2.—W. P. P., a Negro man, 77 years of age, entered the hospital complaining of gradually increasing shortness of breath of six months' duration. The dyspnea was more noticeable on exertion, and occasionally there had been paroxysmal nocturnal dyspnea. During the past year the patient had had two attacks of precordial pain and a diagnosis of coronary thrombosis was made. The patient was known to have had hypertension for five years, the highest recorded blood pressure being 265/140. Two days before admission he complained of pain in the right side of the chest and coughed up small amounts of faintly blood-tinged sputum.

On admission the patient was found to be poorly nourished, drowsy, and cyanotic about the lips, tongue, and nail beds. The temperature was 37.4° C.; pulse, 100; respirations, 36; and blood pressure, 184/120. There were râles at the bases of both lungs, but there was no evidence of consolidation. The heart sounds were distant and the rhythm regular. There was slight pitting edema of the ankles. Reactions to the laboratory tests were negative. The electrocardiograms showed right bundle branch block and a recent anterior and apical infarct. The patient remained afebrile and was given digitalis. He became progressively more lethargic and died quietly on the fourth hospital day.

At autopsy there was found a recent thrombus superimposed on a remote recanalized occlusion of the descending ramus of the left coronary artery with recent and remote infarcts of the anterior and apical portions of the left ventricle, interventricular septum, and apex of the right ventricle. Mural thrombi were present in the left and right ventricles and the left auricle. The heart weighed 500 grams and there was marked stenosing coronary arteriosclerosis. In the lower lobe of the right lung there was a partially organized bronchopneumonia. Hemorrhagic infarcts were present in both the upper and lower lobes of the right lung. The kidneys showed marked arterial and arteriolar sclerosis.

Both common iliac arteries were the seat of advanced arteriosclerosis. In the right iliac artery there was a large intimal hematoma nearly a centimeter in diameter composed of moderately firm but friable, dark reddish-brown blood clot with a narrow peripheral zone of yellow discoloration. Since the hematoma bulged outward it produced only slight obstruction of the lumen of the vessel. At no point was the thickened intima broken, and there was no thrombus (Fig 2).

The left common iliac artery showed numerous hematomas in the intima, but none were as huge as the one on the right side. At one point there was a large, partially discolored thrombus firmly attached to the intima and overlying one of the hematomas, but not communicating with it (Fig 2). The lumen was reduced about 60 per cent by this thrombus.

The aorta showed advanced arteriosclerosis with large mural thrombi just distal to the orifices of the left subclavian artery and the celiac axis. The orifice of the right renal artery was partially obstructed.

The sections from both iliac arteries showed great fibrous thickening of the intima. The thickened portions were relatively acellular and avascular and often were hyalinized. Occasional small collections of fat-laden phagocytes were encountered. The hematomas contained amorphous acidophilic material intermixed with degenerated and hemolyzed erythrocytes. No organization was seen. The huge hematoma in the right iliac artery lay entirely in the intima, and the media and elastica were compressed into a narrow limiting membrane at the periphery. The intima was everywhere intact.

In the left common iliac artery the hematomas also lay in the intima with the exception of one which was in the media. Although the thrombus lay over one of the intimal hematomas the intima was intact and there was no demonstrable rupture (Fig. 3). Early organization had taken place along the line of attachment to the thickened intima.

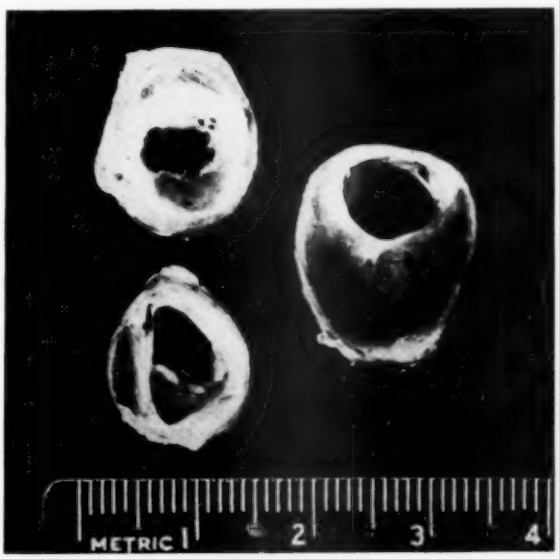

Fig. 2.—Case 2. A large hematoma in the intima of the left common iliac artery (right) with smaller hemorrhages further along the course of the artery (left). The lower section on the left also contains a mural thrombus.

CASE 3.—B. K., a white man, 90 years of age, stated that one week before admission to the hospital, while lying in bed, he suddenly developed a very severe, sharp, shooting pain in the left leg. The pain persisted, becoming more severe, and after several days the patient noticed that his leg was changing color, becoming deep purple. Hypertension was known to have been present for several years.

On admission the temperature was 39.4° C.; pulse, 110; respiration, 40; and blood pressure, 185/85. Physical examination showed a mucopurulent discharge in the posterior pharynx and signs of consolidation at the bases of both lungs. There was marked pulmonary emphysema. Pitting edema was present in both legs. There was ischemic necrosis (dry gangrene) of the left foot and leg extending two-thirds of the way to the knee. All pulses in this leg were absent. The white blood cells numbered 15,800 per c. mm.; the differential count showed normal values. The blood urea nitrogen value was 24.8 mg. per 100 c.c. of blood. There were numerous casts and red blood cells in the urine. The sputum contained pus and many gram-positive diplococci which could not be typed. The electrocardiograms showed auricular fibrillation with digitalis effect, and x-ray examination of the chest showed bronchopneumonia of the upper and middle lobes of the right lung. The patient became lethargic and developed stupor two days before his death, which occurred on the seventh hospital day.

At autopsy there was found extensive bronchopneumonia in all lobes of both lungs. The heart weighed 530 grams and at the apex of the right ventricle there was a small recent infarct, 1 cm. in diameter. The kidneys were the seat of arterial and arteriolar sclerosis and weighed 125 grams each.

Fig. 3.—Case 2. Section from left common iliac artery with two hemorrhages in the diseased intima (bottom) and a large thrombus overlying them. (Hematoxylin and eosin stain, ×20.)

The left external iliac, left femoral, and left popliteal arteries were the seat of severe arteriosclerosis, having thick, partly calcified walls. The intimal surfaces showed numerous irregular yellow plaques with rough surfaces. In the midportion of the femoral artery the lumen was filled with a friable, yellowish-pink mass which was only slightly adherent to the wall and extended for a distance of approximately 10 centimeters. Distal to this the lumen contained a soft, uniformly dark-red, post-mortem blood clot.

Microscopic examination showed occlusion of the lumen by a recent thrombus composed of a partially necrotic fibrin clot rich in hemolyzed and degenerated erythrocytes and leucocytes. At the edges there was an occasional small area showing proliferation of fibroblasts and angioblasts.

The wall of the artery was very thick, especially the intima, and in an occasional situation there were focal hemorrhages immediately beneath the endothelium. The most conspicuous change, however, was found in the media, where there were two large hematomas and several

small ones which were filled with well-preserved erythrocytes and showed no evidence of organization (Fig. 4). Numerous dilated blood vessels engorged with erythrocytes and lined by a single layer of flattened epithelium surrounded these hematomas. Throughout the media there was both diffuse and focal exudation of lymphocytes, plasma cells, and occasional eosinophiles and polymorphonuclear neutrophiles. In a few places calcification had occurred. The vasa vasorum showed moderate thickening of the intima and reduction in the size of the lumina.

Fig. 4.—Case 3. Section from left femoral artery. Two hematomas (bottom and top) and numerous dilated vascular spaces in the media with thrombosis of the lumen. The blood has washed out of the hematoma at the top of the photograph leaving an empty space. (Hematoxylin and eosin stain, ×20.)

DISCUSSION

The changes in the iliac and femoral arteries of these patients are identical with those which are known to occur in the coronary, pulmonary, cerebral, and renal arteries and in the aorta. Vascularization of the intima occurs frequently in association with arteriosclerosis and is often accompanied by profuse bleeding which may lead to the formation of large hematomas which may obstruct the lumen of the vessel by virtue of their size or may rupture and form a thrombus

at the point of rupture. The sequence of events appears to be the same no matter what artery is involved, and the arteries of the lower extremities are no exception.

Vascularization and hemorrhage occur most commonly in the intima but occasionally are found in the media (Case 3), and the resulting dissection of the muscular coats is liable to result in an aneurysm. It seems likely that bleeding in the media, like bleeding in the intima, occurs only in a previously diseased artery. The hemorrhage is the result and not the cause of disease.

The discovery of many thin-walled capillaries in the sclerotic arteries in these three cases lends additional support to the idea, which now seems to be a well-established fact, that the hemorrhages result from the rupture of these capillaries which then bleed into the wall of the vessel, and not from dissection of blood into broken atheromatous plaques as was previously thought. The origin of these capillaries is not always apparent, but it seems likely that most of them arise either from the vasa vasorum or from the main arterial lumens.

It is an interesting observation that in these patients the arterial disease in the vessels of the lower extremities was only a part of a generalized arteriosclerosis which also caused serious manifestations in other organs. All had marked hypertension with vascular disease of the kidneys, two showed advanced sclerosis of the aorta with thrombosis, and one had both recent and remote occlusions of the coronary arteries with multiple myocardial infarcts. Such data indicate that in some patients vascular disease of the lower extremities may merely be one manifestation of a generalized disease process. It may be a most important manifestation, and the one which drives the patient to seek medical aid, but it also may be an indication of much more serious arterial disease elsewhere, for instance, in the coronary arteries.

SUMMARY

Three cases of obstructive arteriosclerosis of the iliac and femoral arteries associated with extensive vascularization of the arterial wall have been described. Bleeding had occurred in all three patients and this led either to the formation of a large hematoma with obstruction of the lumen by pressure or to rupture and thrombosis. The identity of these lesions with those which occur in the coronary, pulmonary, cerebral, carotid, and renal arteries and aorta, is stressed and it is pointed out that arteriosclerosis produces similar lesions no matter which artery it affects. Although the incidence of bleeding into the walls of the peripheral arteries of the lower extremities is not known, nevertheless it seems likely that it is common and that it is a frequent cause of thrombosis just as it is in the coronary arteries. In these patients the arterial disease in the lower extremities was but a part of a generalized arteriosclerosis. Serious disease of the vessels of the heart and kidneys was found in all. In some patients arterial disease of the legs may be an indication of more serious vascular lesions elsewhere, especially in the heart.

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FURTHER OBSERVATIONS ON VAGAL INFLUENCES ON THE HEART DURING ELECTROSHOCK THERAPY FOR MENTAL DISEASE

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PREVIOUS work by a number of authors has demonstrated the common occurrence of arrhythmias immediately after electroshock treatments for mental disease.[1-5] These cardiac irregularities for the most part are the consequence of vagal hyperactivity.[5] The present study is an attempt to analyze further the mechanisms responsible for these changes.

MATERIAL AND METHODS

Ten patients, ranging in age from 36 to 62 years, were studied; none had evidence of organic heart disease although in two of them electrocardiograms revealed right and left bundle branch block, respectively. Tracings, using limb leads, were made before, and continuously during and after administration of shock, each patient being studied on from one to eleven occasions. In each of seven of the patients one record was obtained after the administration of shocks which did not result in a seizure; in all the patients one or more records were obtained during and after induced seizures.

RESULTS

Electroshock Not Resulting in Seizures.—In five of seven patients so studied, bradycardia developed, beginning several seconds after passage of the electricity into the brain, and progressing to reach a maximum six to twelve seconds after administration of the shocks. Slight lengthening of the P-R interval occurred in two instances. The patient in whom the most marked effect occurred happened to be one with bundle branch block (Fig. 1,*B*); in this instance nodal beats and bigeminy occurred when the rate fell to 30 to 40 per minute. A slight change in the form of the QRS complex was noted. In all cases in which bradycardia developed, the rate and rhythm returned to normal in less than one minute after the administration of electroshock.

Electroshock Resulting in Seizures.—It was not possible to secure records during the greater part of the induced seizures but in each instance in this group satisfactory tracings were obtained during the terminal, clonic phases of the convulsions. In every case regular tachycardia occurred and was detectable in spite of the action currents recorded as a consequence of the activity of skeletal

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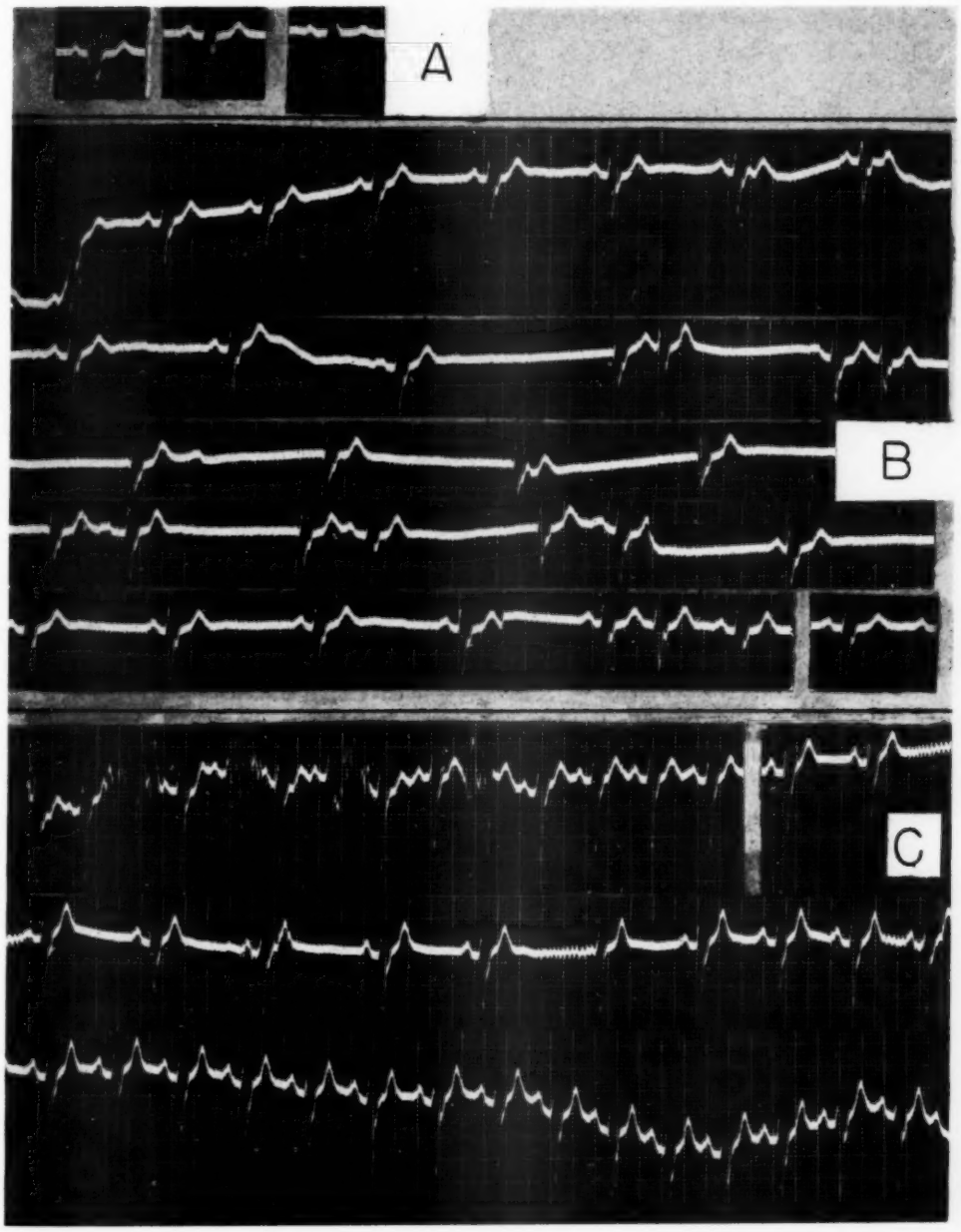

Fig. 1-*A*, Control tracing—three standard limb leads. *B*, Tracing (Lead II) beginning one second after administration of electroshock, but without development of a convulsion. The gap in the last line of this section indicates three additional seconds of unchanged rate and rhythm. *C*, Tracing (Lead II) during and after the end of the clonic phase of an induced seizure. Action currents of skeletal muscle contractions are seen masking some of the cardiac action currents in the first portion. The gap in the first line indicates two additional seconds of unchanged rate and rhythm before the onset of hyperventilation.

muscle (Fig. 1,*C*). The tachycardia continued until breathing, absent during the convulsions, was ushered in again with deep respirations. With the onset of hyperventilation, bradycardia, sinoauricular block, sinus arrhythmia, nodal beats, auricular premature beats, or slight prolongation of the P-R interval, or any combination of them, occurred for from two to fifteen seconds; thereafter regular rhythm was uniformly found and the rates were almost always rapid. In patients with bundle branch block no significant changes in form of the QRS complexes occurred except for the rhythmical variation associated with respiration described previously.[5]

DISCUSSION

The present study corroborates earlier work,[1-5] as to the occurrence of arrhythmias, which resemble the effects of vagal excitation, in association with electrically induced convulsions; these arrhythmias are known to be prevented by the previous administration of atropine.[1,5] In addition, the work described here suggests two mechanisms as explanations for the changes found.

The vagal hyperactivity responsible for the arrhythmias seen immediately after the seizures apparently is related temporally to the onset of hyperventilation, the cardiac irregularities appearing immediately after the resumption of breathing; the arrythmia, therefore, may be consequent to reflexes activated when large amounts of blood, trapped in the periphery during the seizure,[7] are sucked into the great veins and right auricle. No such mechanism, however, can account for the early vagal activation seen after electroshock but in the absence of seizures; respiration in these instances is usually depressed and is slow, shallow, and irregular. The possibility exists that direct stimulation of intracranial areas which influence cardiac rate through the vagus occurs. A possible alternative explanation is stimulation of hypothalamic centers through the release into the spinal fluid of secretion of the posterior lobe of the pituitary gland as described by Cushing and his group.[8-10] The delayed onset of vagal effects on the heart after electroshock without subsequent seizures, together with the appearance of cutaneous vasodilatation, lacrimation, salivation, and piloerection at approximately the same time suggests the possibility that Cushing's mechanism[8-10] is involved. Usually the arrhythmias associated with electroshock therapy are mild in degree, short in duration, and of no consequence. Occasionally, however, the arrhythmias which occur are of clinical importance. A number of instances have been reported in the literature or by word of mouth in which individuals, with no evidence of visceral disease, died during electroshock treatments; autopsy revealed no cause for this accident. In our own experience this has not occurred, although two patients apparently came close to death. After the first seizure in each case the heart was irregular with a rate of 10 to 30 per minute, but after an unmeasured interval it resumed its normal beat and went on to the usual tachycardia. Each of these patients was studied two days later and an abnormally sensitive carotid sinus mechanism was demonstrated; thereafter each was given 0.8 mg. of atropine sulfate subcutaneously twenty minutes before each succeeding treatment and experienced no further difficulty. Since then the routine examination of patients before shock therapy

at this hospital includes testing of the carotid sinus mechanism, and all patients with abnormally sensitive mechanisms are given atropine before each electroshock treatment. No further untoward event has occurred. The vagal arrhythmias of electroshock therapy are of particular importance in patients given curare in order to modify the severity of the seizures, for curare alkaloids inhibit cholinesterase and so may accentuate vagal phenomena dangerously.[11]

SUMMARY AND CONCLUSIONS

The vagal hyperactivity which often causes cardiac arrhythmias in patients given electroshock therapy is apparently the consequence of more than one mechanism. Passage of electricity through the cranium activates a mechanism which results in vagal stimulation; this is usually masked by the tachycardia which occurs during electrically induced seizures. After the end of such convulsions there is marked hyperventilation which ushers in another period of vagal hyperactivity which may be reflex in origin. The importance of testing for carotid sinus hypersensitivity before treatment, and the use of atropine to prevent dangerously excessive vagal activity, is pointed out.

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QUANTITATIVE BLOOD FLOW MEASURED CALORIMETRICALLY IN THE HUMAN TOE IN NORMAL SUBJECTS AND IN PATIENTS WITH RESIDUA OF TRENCH FOOT AND FROSTBITE

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TRENCH foot was first described in 1812 by Napoleon's Surgeon General, Baron D. J. Larrey,[1] in soldiers returning from the Russian campaign. Since that time the subject has been of increasing importance in military, naval, and also civilian medicine. Numerous clinical and pathologic, as well as some experimental, investigations have been carried out.[2] It is generally agreed that trench foot, chilblains, and erythrocyanosis are similar pathologically, whereas frostbite belongs in a different category and is due to actual freezing of tissues.[3] In some cases, however, it is possible for frostbite and trench foot to occur together and when gangrene supervenes in trench foot the pathologic changes may be difficult to distinguish from those of severe frostbite.[4]

In trench foot the injury seems to involve chiefly nerve and muscle tissue.[5] The blood vessels are affected only in that their permeability is increased, the reaction being that of "aseptic" inflammation.[5] When the skin is broken, secondary bacterial infection may supervene.[4] Thromboses in major vessels including arteries appear to occur as secondary phenomena in the wake of gangrene.[4]

In frostbite, on the other hand, if the process is sufficiently prolonged, the increased permeability of the small vessels, together with extreme vasoconstriction, causes loss of plasma from the vessels with a remaining obstructive sludge of red cells.[6] These cells may be swept into the veins when the circulation reopens or may be fixed sufficiently to produce permanent obstruction.[7] It is believed by some[8] and denied by others[9] that this vascular obstruction can be prevented by timely administration of heparin. When frostbite produces gangrene, fibrinous thrombosis may occur secondarily as in trench foot.[10]

The neurovascular responses of the human skin to the stimulus of cold are described in detail by Sir Thomas Lewis.[3] A physiologic approach to the study of trench foot itself was made in 1945 by Schechter and Ragan[11] who used ischemic pain as an index of the severity of the injury. In 1946 Paddock[12] studied patients one to two years after their recovery from trench foot and found evidence of persistent nerve and muscle lesions as manifested by sensory changes and muscu-

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lar weakness. He also measured skin temperatures and noted color changes after the production of hyperemia by the application of direct and indirect heat, but could find no evidence of vascular obstruction in most of his patients. In 1947, Burch, Myers, Porter, and Schaffer[13] reported extensive physiologic studies in patients with trench foot designed to determine whether the presence of low-grade inflammation could be demonstrated. They measured the degree of reactive hyperemia under exacting conditions of room temperature and covering after a fixed period of vascular occlusion of the leg with a pressure cuff, and attempted to classify their patients on the basis of these reactions.

It was our purpose to determine how much of a role actual vascular obstruction played in the residual symptomatology of trench foot and frostbite and to see whether this obstruction could be measured quantitatively. The calorimetric method had been employed only for measuring maximum blood flow in the finger tip.[14] It was believed feasible to adapt this method to the measurement of blood flow in the big toe and to establish normal standards for maximal flow. These values could then be compared with those obtained in patients with residual symptoms of trench foot or frostbite.

METHOD

The method for measuring blood flow in the toe had to be modified to some extent from that used for the finger tip. The calorimeter cup held 200 c.c. instead of 100 c.c. of water and was constructed in such a manner that the diameter of the cup was approximately the same as its height. The apertures for the toe, tirring device, and Beckmann thermometer are shown in Fig. 1. The eccentric position of the aperture for the toe made it possible to insert the big toe up to the first crease, the other toes being separated from the cup by means of dry absorbent cotton.

Blood flow was calculated from the formula:

$$F = \frac{(\Delta t_1 + \Delta t_2)\ (m + e)}{s\ a\ (t_3 - t_4)}$$

in which $F =$ blood flow in grams per square centimeter per minute; $\Delta t_1 =$ rise in temperature per minute with the toe inserted; $\Delta t_2 =$ fall in temperature per minute with a cork in place of the toe; $m =$ the volume or weight of the water in the cup; $e =$ the hydrothermic equivalent of the cup, thermometer, stirrer, and toe; $s =$ the specific heat of the blood; $a =$ the area of the immersed toe; $t_3 =$ mouth temperature; and $t_4 =$ average calorimeter temperature during the period of measurement.

Blood pressure in the toe was measured with a Gaertner capsule as in the finger. The systolic pressure was easily ascertained by blanching the toe with a rubber band, inflating the cuff of the Gaertner capsule above systolic pressure, cutting the rubber band, lowering the pressure, and noting the point at which flushing appeared in the tip of the toe. The diastolic pressure, ascertained by the method of checking the point of cessation of throbbing, was unsatisfactory.

All studies were done after reflex vasodilatation by heat. This was administered by an electric-bulb cradle which was placed over the trunk of the patient

and covered by blankets. It was found necessary to heat the trunk for forty-five to ninety minutes in order to produce satisfactory vasodilatation of the toe, in contrast to the twenty to thirty minutes which usually sufficed for the finger. All abnormally low readings were verified by repeating the test. In an occasional patient with anxiety, both in the normal and trench foot group, normal readings were obtained only in the second test. In the remaining subjects the discrepancy between the results of the first and second test was small.

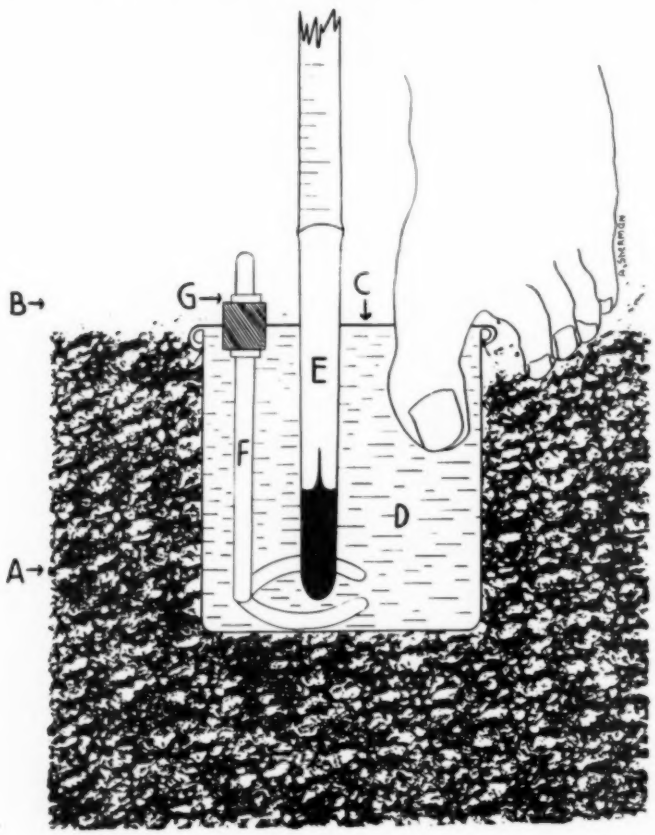

Fig. 1.—Apparatus used in determination of blood flow in the toe. *A*, broken cork in wood box; *B*, absorbent cotton; *C*, rubber membrane held in place over lip of cup by rubber band; *D*, approximately 200 c.c. of water in polished aluminum cup; *E*, Beckmann thermometer; *F*, hand stirrer; *G*, glass and rubber jacket for stirrer.

The patients studied were those who appeared at the New York Regional Office Clinic of the Veterans Administration claiming disability for trench foot, frostbite, or both. At the same time a series of patients with presumably normal blood vessels were studied including several with anxiety reactions. Only one woman was included. In some patients circulation was measured in both the right and left big toes but in most that side was selected where the symptoms were most pronounced.

RESULTS

The results are presented in Tables I and II. Since the calorimeter measures gram calories, blood flow is expressed as grams per square centimeter per minute. These values can be converted to cubic centimeters per square centimeter per minute by dividing by the specific gravity of blood. When two tests were performed, only the second test was used for statistical computation. If measurements were made on two toes of the same patient, the lower of these was used in the statistical analysis.

The normal blood flow in the toe varied from 0.14 to 0.27 grams per square centimeter per minute. The average blood flow was 0.191 ± standard deviation of 0.041. The decreased average blood flow in the toe as against that in the finger is in accord with the observations of other workers.[15] No attempt is made here to estimate the peripheral resistance in the toe.

TABLE I. NORMAL SUBJECTS

PATIENT	TEST NO.	AGE IN YEARS	SEX	BLOOD FLOW (GRAMS/SQ. CM./MIN.)	DIGITAL BLOOD PRESSURE (SYSTOLIC) (MM. HG)
1		35	M	0.18	72
2		41	M	0.15	112
3		21	M	0.24	101
4		24	M	0.25	95
5		28	M	0.15	82
6		24	F	0.20	88
7		24	M	0.26	92
8		26	M	0.16	92
9		21	M	0.16	84
10		38	M	0.23	102
11		38	M	0.16	104
12		24	M	0.25	98
13		40	M	0.14	78
14		40	M	0.16	92
15		32	M	0.21	78
16		30	M	0.16	65
17		32	M	0.14	78
18	1	36	M	0.10	108
	2			0.15	80
19		27	M	0.27	60
20		31	M	0.18	64
21		32	M	0.23	60
22		31	M	0.19	90
23		28	M	0.17	88

In the patients with residual symptoms of trench foot or frostbite the average blood flow was 0.155 grams per square centimeter per minute ± standard deviation of 0.045. Twenty-seven per cent of these patients had blood flow readings below the lower limit of normal, most of these low readings having been verified by second tests. In one patient who had experienced severe frostbite, anesthesia was persistent and it was impossible to achieve sufficient vasodilatation to record anything but minimal blood flow in the toes. This patient was not included in our series. Thirty-two per cent of the patients with trench foot or frostbite had

TABLE II. PATIENTS WITH RESIDUAL SYMPTOMS OF TRENCH FOOT AND FROSTBITE

PATIENT	TEST NO.	AGE IN YEARS	SEX	BLOOD FLOW (GRAMS/SQ. CM./MIN.)	DIGITAL BLOOD PRESSURE (SYSTOLIC) (MM. HG)
1		23	M	0.20	90
2		28	M	0.18	96
3		22	M	0.14	80
4		26	M	0.23	58
5		23	M	0.11	68
6		22	M	0.13	86
7		31	M	0.16	88
8		25	M	0.14	84
9		22	M	0.15	88
10		24	M	0.15	86
11	1	25	M	0.09	60
	2			0.16	60
12	1	35	M	0.11	60
	2			0.11	60
	3			0.11 left	60
				0.11 right	74
13	1	23	M	0.03	70
	2			0.02	90
14		23	M	0.14	88
15		22	M	0.08	78
16	1	32	M	0.07	86
	2			0.10	96
17		33	M	0.15	76
18		28	M	0.14	90
19		34	M	0.17	78
20		29	M	0.11	110
21	1	29	M	0.11	90
	2			0.11	78
22		21	M	0.24	102
23	1	32	M	0.10	94
	2			0.06	90
24		21	M	0.18	78
25	1	23	M	0.13	84
	2			0.21	74
26	1	35	M	0.06	90
	2			0.21 left	88
				0.20 right	88
27		34	M	0.20 left	90
				0.23 right	84
28		30	M	0.19	102
29		23	M	0.17	118
30		26	M	0.20	98
31		24	M	0.15	90
32		38	M	0.23	98
33		33	M	0.17	72
34		30	M	0.21	114
35		32	M	0.15	70
36		33	M	0.15	70
37		22	M	0.19	74
38	1	32	M	0.11	100
	2			0.15	84
39	1	39	M	0.17 left	78
				0.11 right	62
	2			0.13 right	58
40		36	M	0.18	94
41	1	25	M	0.08	90
	2			0.12	76

blood flows in the low normal range (0.14 to 0.17 grams per square centimeter per minute). No significant difference in the incidence of low blood flow was noted in the patients with residual frostbite as against trench foot.

To test the reliability of these statistics $\frac{x}{\sigma}$ was determined. If $\overline{X}_1 =$ the arithmetic mean of the normal group and $\overline{X}_2 =$ the arithmetic mean of the abnormal group, then $x = \overline{X}_1 - \overline{X}_2$. σ is the standard error of the difference between the two means and is obtained by the formula, $\sigma_{\bar{x}1 - \bar{x}2} = \sqrt{\sigma_{\bar{x}1}^2 + \sigma_{\bar{x}2}^2}$. $\sigma_{\bar{x}1} = \frac{\sigma_1}{\sqrt{N_1}}$ in which σ_1 is the standard deviation of the normal group and N_1, the number of patients in that group. $\sigma_{\bar{x}2}$ is determined similarly for the abnormal group. By this method $\frac{x}{\sigma}$ was found to be 3.16, the difference between the two groups being hence clearly significant.

The decreased blood flow observed in these patients might be attributed to failure to achieve maximal vasodilatation because of persistent nerve lesions. It is to be pointed out, however, that in the patients reported here demonstrable sensory and motor nerve lesions were absent. It is more likely, therefore, that the diminished blood flow represents actual obstruction of the small arterial channels of the foot. This obstruction may be due to initial occlusion of blood vessels by sludge as in frostbite,[9] to secondary thromboses,[4,10] or to the contraction of perivascular scar tissue.[15]

SUMMARY

1. Blood flow in the human toe after vasodilatation by heat was studied calorimetrically in a group of twenty-three normal subjects and in a group of forty-one patients with residual symptoms of trench foot and frostbite.

2. The average normal blood flow was 0.191 grams per square centimeter per minute ± standard deviation of 0.041.

3. The average blood flow in patients with trench foot and frostbite was 0.155 grams per square centimeter per minute ± standard deviation of 0.045.

4. The significantly decreased blood flow in the latter group is believed to be attributable to organic obstruction or constriction of the small arteries of the foot.

The cooperation of Dr. Adrian G. Gould, Medical Director of the New York Regional Office Clinic, Veterans Administration, in making facilities available for this work is gratefully acknowledged. We are also indebted to Mr. Gilbert Grossinger for technical assistance.

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FIVE-MINUTE ARTERIAL OCCLUSION TECHNIQUE FOR THE DETERMINATION OF VASCULAR INSUFFICIENCY

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INTRODUCTION

THE use of venous occlusion plethysmography in the study of vascular disorders of the foot and toe has received considerable impetus in the American literature during the past ten years. The results of these studies have been summarized in Table I. It is generally agreed that the resting blood flow values have a considerable variation and that the augmented flow readings are a more consistent indication of the status of the vessels. The production of augmented blood flow by the use of prolonged body heating, prolonged local heat, or prolonged arterial occlusion is not without disadvantages in elderly or debilitated patients with gangrene or trophic changes in the feet and toes. Therefore the purpose of this study was to determine whether arterial occlusion of the foot for a moderate period of time (five minutes) was adequate to differentiate various grades of arteriosclerotic arterial insufficiency from normal control subjects.

APPARATUS

A plastic pneumoplethysmographic boot* (Fig. 1) which permitted visualization of the color and position of the foot during the tests was designed and constructed. This instrument utilized many of the features of a glass small-animal pneumoplethysmograph developed previously.[12] In order to reduce the air space within the instrument, the boot was constructed in two half shells which were bolted together around the foot. By this means the foot could be inserted into the apparatus and the air space surrounding the ankle and foot kept at a minimum. Records of high sensitivity were made possible by this instrument. The foot was sealed into the chamber by means of a rubber dam placed at the ankle. A venous occlusion cuff one inch in width was placed at the ankle proximal to the plethysmograph. This cuff was inflated by connection with a pressure reservoir tank which was maintained at 50 to 70 mm. of mercury. When the cuff was inflated a signal magnet was activated, and this moment was accurately recorded on the film time-line strip. Increase in volume of the foot was recorded by a modi-

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*Constructed by J. Hageman.

TABLE I

YEAR	AUTHOR	TYPE OF INSTRUMENT	METHOD	SUBJECT	NUMBER	RATE OF FLOW IN C.C PER MIN. PER 100 C.C		
						AVERAGE	MAXIMUM	MINIMUM
1938	Kunkel and Stead[1]	Water-filled boot with Brodie bellows	Water in boot heated to 43° C. to produce maximum vasodilation.	Normal age, 17 to 67 years	(34)	17.1	25.9	11.1
				Arteriosclerosis without symptoms or trophic change	(10)	8.0		
				Arteriosclerosis with symptoms or trophic changes	(11)	4.8		
				Thromboangiitis obliterans	(5)	10.3	24.9	4.9
1938	Killian and Oclassen[2]	Water-filled boot with Brodie bellows	Water in boot at room temperature	Normal, age, 21 to 32 years	(9)		4.2	0.9
			Water in boot at 40° C.				14.8	6.4
			Mustard bath at 40° C.				13.2	7.3
1939	Abramson, Zazeela, and Marrus[3]	Water-filled boot with Brodie bellows	Water in boot at 32° C.	Normal	(1)	4.9		
			Reflex vasodilation and boot at 32° C.			10.1		
			Water in boot at 45° C.			15.2		
1939	Kunkle, Stead, and Weiss[4]	Water-filled boot with Brodie bellows	Water in boot at 32° C.	Normal	(4)	Less than 3		
			Water in boot at 37° C.	Normal	(4)	Around 5		
			Water in boot at 43° C.	Normal	(34)	17		
1939	Abramson, Zazeela, and Oppenheimer[5]	Water-filled boot with Brodie bellows	Water in boot at 45° C.	Normal	(14)	11.6	25.5	6.8
1940	Stead and Kunkel[6]	Water-filled boot with Brodie bellows	Water in boot at 43° C. and body heating	Normal	(38)	17.1		
				Normal, age, 30 to 39 years		19.5		
				Normal, age, 40 to 49 years		18		
				Hypertension	(16)	21.7	34	14
				Hypertension, age, 30 to 39 years		18		
				Hypertension, age, 40 to 49 years		22		

1940	Wright and Phelps[7]	3200 c.c. capacity aluminum boot with optical recording	Room temperature Boot in water bath at 45° C. Sacral diathermy	Normal	(1)	4.2 11.7 2.7		
1942	Landowne and Katz[8]	Water-filled boot with Brodie bellows	At room temperature After 10 minutes arterial occlusion	Normal	(13)		6.0 22.5	0.5 6.3
1942	Landowne[9]	Air-filled boot with a water and glycerine dampened spirometer for recording	Room temperature Arterial occlusion ½ to 15 minutes (average 7.5 min.)	Thromboangiitis obliterans	(7)		7.5 7.6	1.1 2.5
1946	Goetz[10]	Toe capsule, air-filled, recording from capillary pipette	Venous occlusion at ankle. Reflex vasodilation	Normals			90 c.c.	1 c.c.
1948	Scheinberg, Dennis, Robertson, and Stead[11]	Water-filled boot with Brodie bellows	Water in boot at 32° C. Resting 5 min. arterial occlusion 10 min. arterial occlusion 15 min. arterial occlusion Venous bed emptied Patient erect	 Normal Normal Normal Normal Normal Normal	 (18) (4) (3) (8) (8) (12)	 4.0 5.8 8.0 10.4 6.4 15.3	 7.8 6.5 9.5 15.3 15.0 39.0	 1.4 4.9 5.2 7.2 3.5 5.0
			Water in boot at 38° C.: Resting 10 min. arterial occlusion 15 min. arterial occlusion	 Normal Normal Normal	 (8) (5) (4)	 8.6 13.4 15.0	 16.0 18.0 17.0	 4.1 9.2 12.0
			Water in boot at 45° C. Resting 5 min. arterial occlusion 10 min. arterial occlusion Venous bed emptied Patient erect	 Normal Normal Normal Normal Normal	 (17) (5) (2) (4) (10)	 16.7 21.1 13.5 16.5 44.0	 34.0 32.8 13.6 19.0 77.0	 7.5 14.9 13.4 13.8 24.0
			Water in boot at 40° C.: Venous bed emptied Patient erect	 Thromboangiitis obliterans Thromboangiitis obliterans	 (1) (1)	 2.7 9.6		

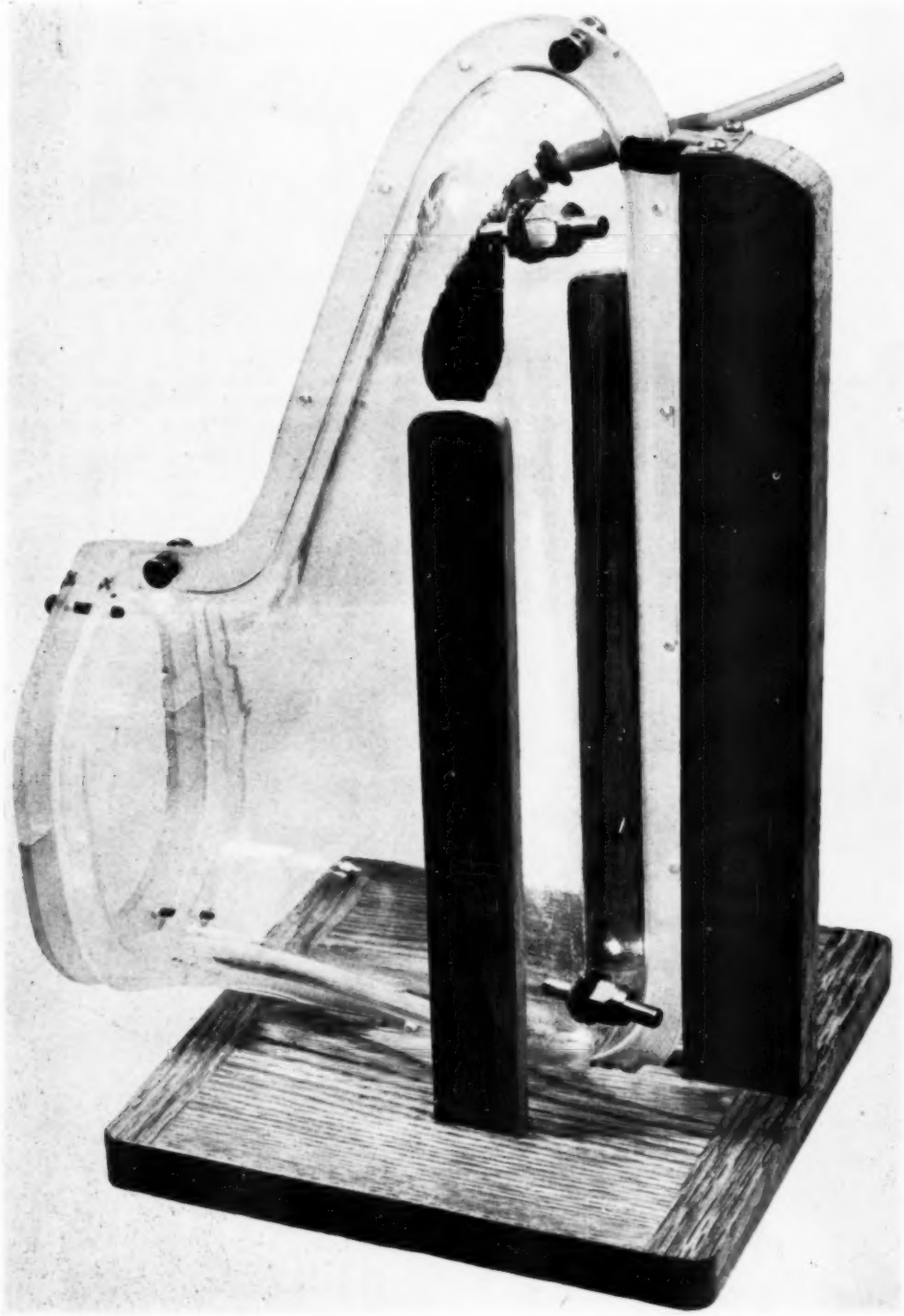

Fig. 1.—Photograph of plastic pneumoplethysmographic foot boot showing calibration balloon and recording outlets. The construction permits the assembly of two half shells around the foot and minimizes air space and ankle aperture.

fied Wiggers' optical recording capsule which utilized a copper-beryllium membrane of 0.005 inch thickness. The recording apparatus was mounted on a Cambridge No. 3 Electrocardiograph. The injection of quantitated amounts of fluid into the plethysmograph balloon served to calibrate the instrument. Throughout the test saturated water vapor was present in the boot in order to minimize the effect of skin evaporation.

For the determination of toe flow, a plastic cup was used. The venous occlusion cuff was placed at the ankle according to the method of Goetz.[10] Recording was by means of the Cambridge Pneumoplethysmograph (Burch-Winsor model).[13]

METHOD

The clinical evaluation of the patient included a history and a general physical examination. Special note was made of the blood pressure, palpation of the peripheral vessels, and oscillometric tests of the calf and foot. The condition of the foot and toes was noted, with particular reference to gangrene or trophic skin abnormalities.

The tests were performed in a quiet room. The temperature and humidity were recorded before, during, and after the tests. Patients who had eaten four to seven hours before were rested one and one-half to two hours. To eliminate the effect of diet, obvious proteins were eliminated from the meal preceding the test. These precautions were taken to insure the basal resting state and to eliminate the postprandial effect of ingested protein.

A series of eight control resting flow determinations were made. Then the arterial occlusion (Ivy-rib) cuff was placed proximal to the knee and inflated to a pressue of 300 mm. Hg for five minutes. This type of cuff placed over the femoral condyles was found to give the most efficient results. The five-minute period was taken in preference to longer periods because of the desire to avoid irreversible tissue damage in the patients having gangrene. The other cases were given the same duration of arterial occlusion in order to obtain comparative results. After the arterial cuff was released, flow measurements were taken at intervals of one minute for a period of ten minutes. The records were calibrated before each set of resting control tracings and again before the postarterial occlusion records. A test of venous occlusion artifact was made during the period of arterial occlusion. The artifact, if present, was adjusted in the calculation of the flow readings. The blood flow was calculated according to the method of Kondo, Katz, Meyer, and Malinow[12] (Fig. 2). Following the tests, the foot volume was determined by immersing the limb in water and measuring the displacement of fluid.

The toe flow technique used was according to the method of Goetz.[10]

RESULTS

Studies of the blood flow in the foot were made in twenty patients (Fig. 3). The control group included six subjects between the ages of twenty-eight and seventy years. The average resting flow was 12.2 c.c. per 100 c.c. limb volume

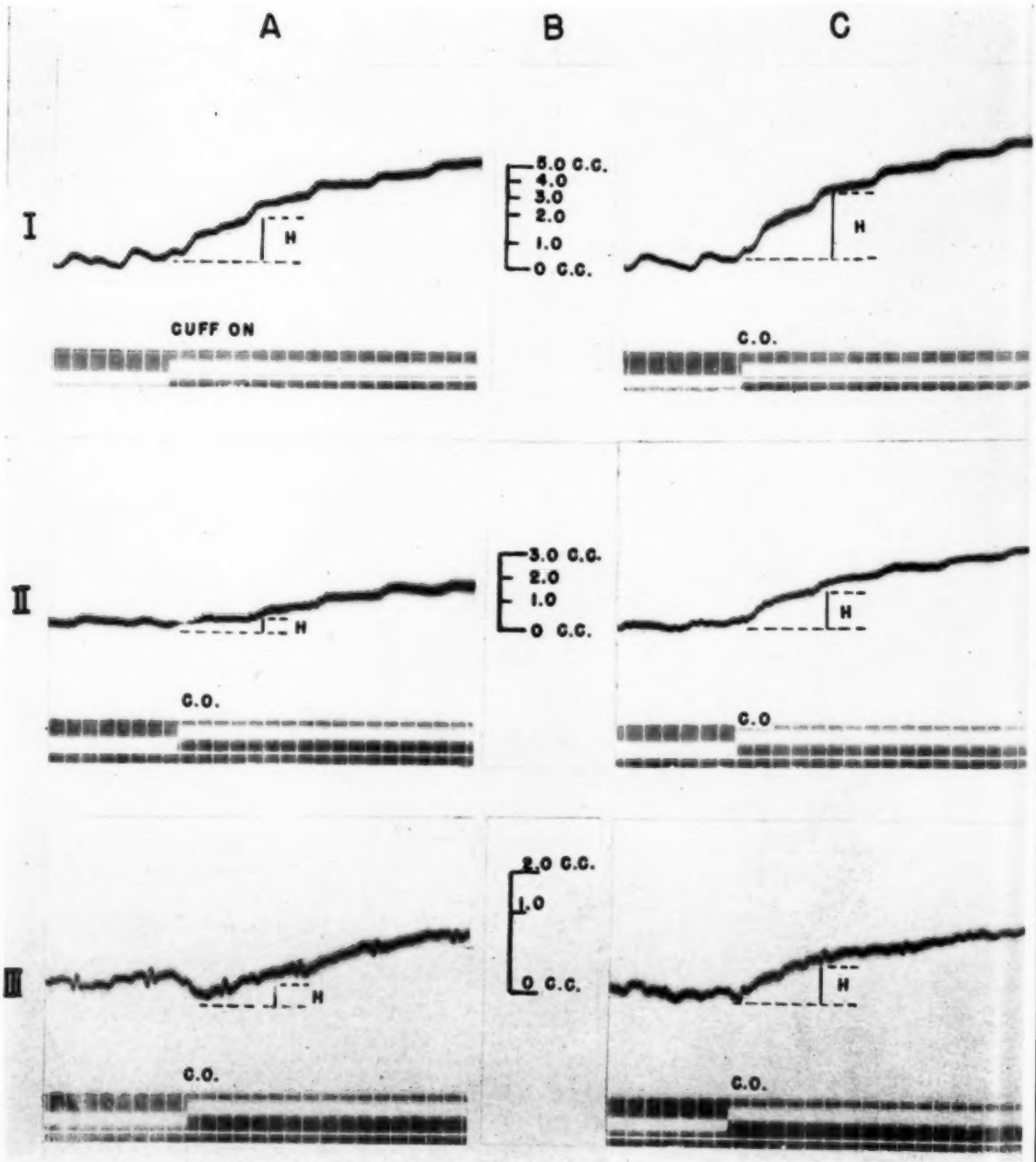

Fig. 2.—Plethysmographic foot blood flow records of: *I*, normal subject, *II* intermediate subject (diminished pedal pulses); and *III*, patient with gangrene of the toe. Column A is before five-minute arterial occlusion and Column C after arterial occlusion. Column B represents calibration of the instrument. (A more sensitive calibration is necessary to record Subjects II and III.) *C.O.* is onset of venous occlusion cuff. Time is recorded in one-fifth second intervals. *H* represents flow during one second. There is a small cuff artifact in Subject I which is adjusted in the final calculation of blood flow.

per minute. The extremes were 4.4 to 28.5 cubic centimeters. After arterial occlusion the average flow was 20.9 c.c. (range 8.3 to 45.5 c.c.). The resting blood flow in the intermediate group having absent peripheral pulses (six patients) due to arteriosclerosis was 4.8 c.c. (range 1.2 to 9.1 c.c.), and the postarterial occlusion flow was 10.2 c.c. (8.3 to 13.4 c.c.). The third group included three

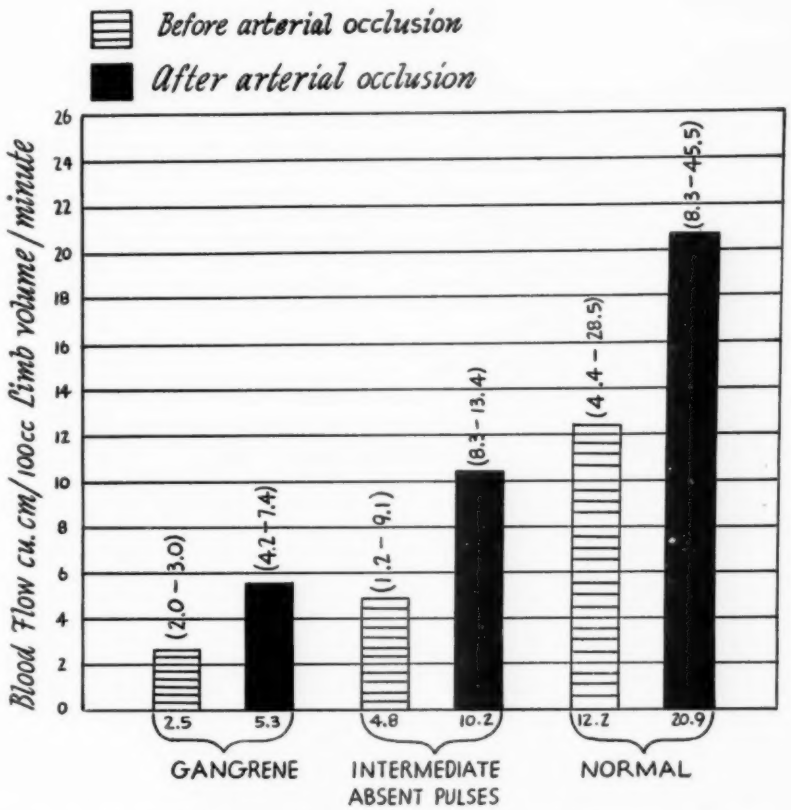

Fig. 3.—Chart of foot blood flow in normal, intermediate, and gangrenus individuals before and after arterial occlusion.

individuals having arteriosclerotic gangrene of the toes; resting flow was 2.5 c.c. (2.0 to 3.0 c.c.) and post occlusion flow was 5.3 c.c. (4.2 to 7.4 c.c.). There is apparent a marked difference in flow between the patients with gangrene and the normal controls. No overlapping of values is present before or after the arterial occlusion test. According to these figures a differentiation is possible between the control and gangrene cases either on the basis of resting or post-arterial occlusion flow readings. The middle group comprising the individuals with impalpable pulses shows intermediate values with regard to resting and hyperemic flow. This group evidently consisted of subjects with all grades of arterial involvement between the normal and gangrenous extremes.

Three patients who had undergone sympathectomy were studied but were considered in a separate category because of the complex nature of the disease. The first patient had abdominal aortic obstruction due to arteriosclerosis, shown by roentgenogram. All leg pulses were absent. Control blood flow averaged 7.1 c.c., and postarterial occlusion flow was 7.8 cubic centimeters. In the second patient (Buerger's disease with absent leg pulses) resting flow was 9.3 c.c. and

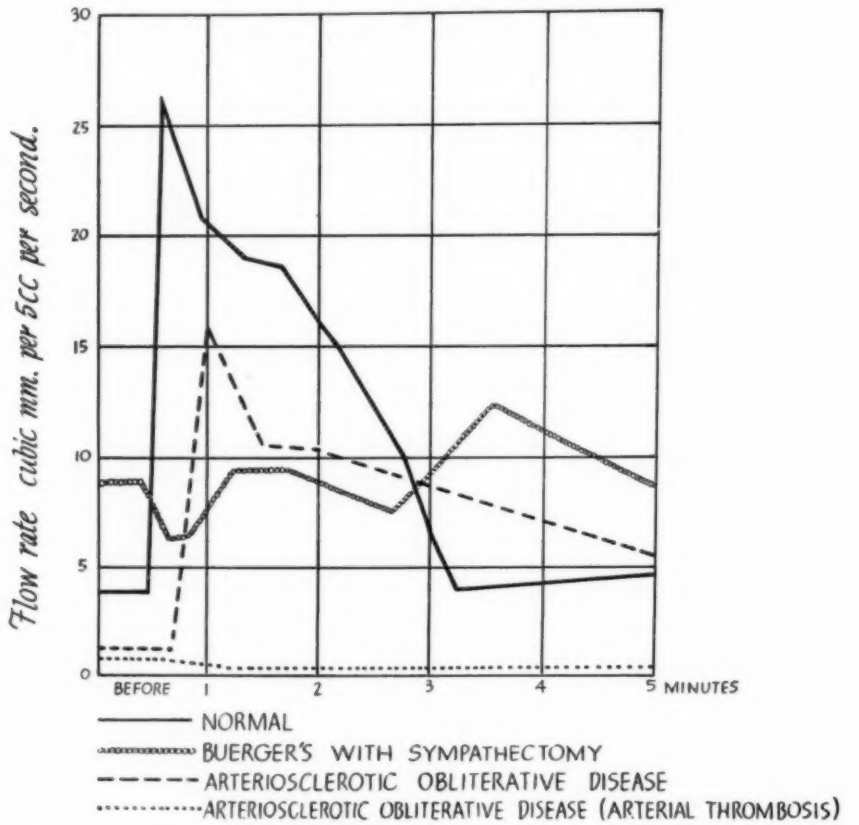

Fig. 4.—Flow records in the toe after arterial occlusion shown by a normal subject and patients with arteriosclerosis obliterans and thromboangiitis obliterans.

hyperemic flow was 12.2 cubic centimeters. Both of these patients had a minimal rise after arterial occlusion attributable to a marked degree of obstruction in the femoral and aortic vessels (Landowne and Katz Phenomenon[8,9]). The third subject had complete severance and ligation of the femoral artery subsequent to a knife wound. All leg vessels demonstrated good pulsations, including the femoral artery distal to the ligation. The resting and hyperemic flow were 6.9 and 13.8 c.c., respectively. The values were within the normal range and serve to illustrate the degree of collateral circulation established by the gluteal and pelvic vessels. A fourth patient having diabetes mellitus and an ulcer of the sole of the foot due

to local skin irritation was studied. The pedal vessels of this patient showed good pulsations. Resting flow was 8.5 c.c. and postarterial occlusion flow was 17.0 cubic centimeters. The figures were within the normal range and demonstrated that the ulcer was not due to generalized vascular disease of the foot.

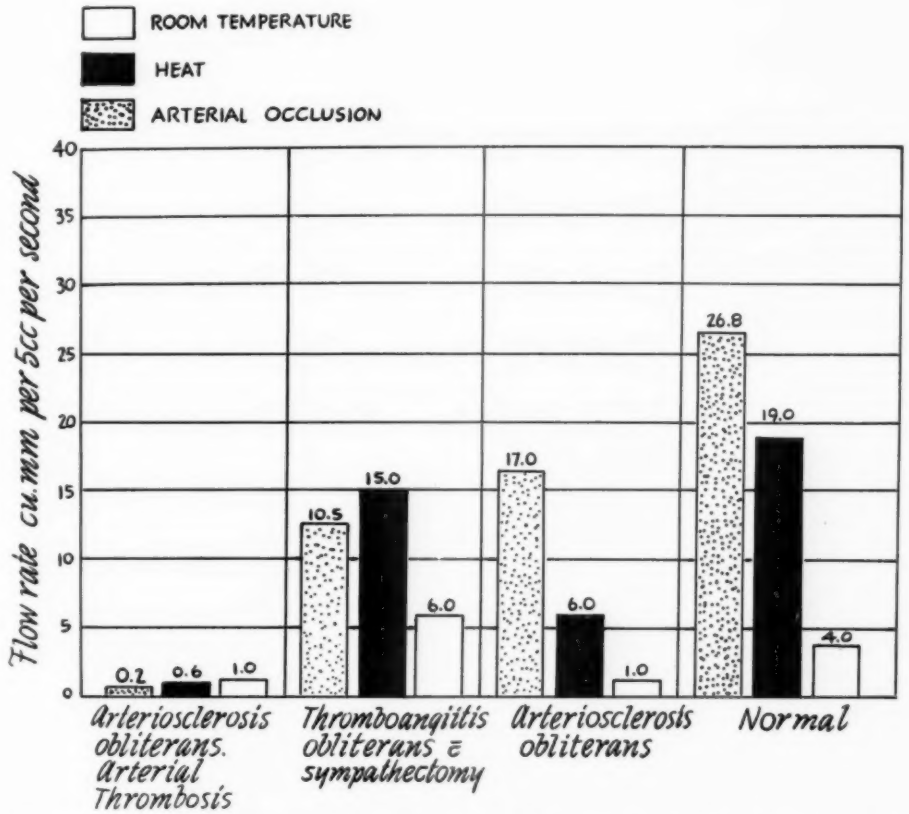

Fig. 5.—Chart showing the comparative effect of heat and arterial occlusion on the subjects with arteriosclerosis obliterans and arterial thrombosis, thromboangiitis obliterans with sympathectomy, arteriosclerosis obliterans, and a normal peripheral vascular system.

Studies of the blood flow in the toe, before and after arterial occlusion, were made in normal control subjects and in those having arteriosclerosis obliterans, thromboangiitis obliterans (with sympathectomy), and arteriosclerotic arterial thrombosis. The results have been tabulated by graph in Figure 4. The high and rapid rise in the blood flow of the normal control subject contrasts with the lower and delayed rise of the arteriosclerotic patient. There was a higher resting flow and a minimal rise in thromboangiitis obliterans with sympathectomy. Finally, the patient with arteriosclerotic arterial thrombosis showed a low resting flow value and an actual fall in flow after arterial occlusion.

A comparative study of heat and arterial occlusion on blood flow in the toe has been included in Figure 5. There was an increase in flow following arterial

occlusion over the value seen with heat in the normal and arteriosclerotic subjects. In the patient with thromboangiitis obliterans with sympathectomy there was an increase in blood flow due to the arterial occlusion technique. This increase was exceeded by that produced by heat.

In the subject with arterial thrombosis there was a fall of blood flow by both arterial occlusion and heat, but the fall in flow due to arterial occlusion was greater.

A study of the variation of 151 plethysmographic blood flow readings in the foot taken on twenty-one resting subjects is shown in Table II. The actual variation in the control group was the greatest. Much less variation was seen in the intermediate group, and the least amount of variation in flow was present in the gangrenous group.

TABLE II.

GROUP	NUMBER OF PATIENTS	NUMBER OF DETERMINATIONS	AVERAGE DEVIATION	STANDARD DEVIATION
Normal	6	48	2.05 c.c.	3.33 c.c.
Intermediate	6	43	0.79 c.c.	0.95 c.c.
Gangrene	4	23	0.46 c.c.	0.67 c.c.
Totals	21	151	1.19 c.c.	2.04 c.c.

DISCUSSION

Following five-minute arterial occlusion a definite rise of blood flow was produced in the foot and toe. This method enabled differentiation to be made between three groups of subjects (normal, intermediate, and the group with arteriosclerotic gangrene). The hyperemic flow readings obtained from the foot are in agreement with those found in the literature.[1-11] The advantage of this method over more prolonged and drastic procedures is seen when patients having tissue damage are studied. The blood flow after five-minute arterial occlusion correlates well with the clinical findings in the normal and abnormal subjects. The highest readings were in the normal group (average 20.9 c.c.); the lowest readings were seen in the presence of gangrene (average 2.5 c.c.); and intermediate readings were obtained in those persons lacking palpable pulses (average 10.2 c.c.).

It is interesting to note that there was some slight increase in blood flow of the foot in the subjects having arteriosclerotic gangrene of the toes. This phenomenon was perhaps due to the irregular involvement of the vessels in the arteriosclerotic process with the sparing of some foot vessels proximal to the necrotic toes. The increase in blood flow would be due to shunting along vessels of the foot which were spared by the arteriosclerotic process. This supposition is borne out by the actual decrease in blood flow to the toe in the subject having arteriosclerotic arterial thrombotic disease (Figs. 4 and 5). The physiologic process in these arteriosclerotic patients differs from that seen in thromboangiitis obliterans. In Buerger's disease the process involves the main arterial trunks supplying the

foot. Landowne and Katz[8,9] have shown that in the presence of severe thromboangiitis obliterans the dilatation of vessels distal to the obstruction does not produce an increase in blood flow below the obstruction. The Landowne-Katz effect was demonstrated by the two patients having aortic and femoral artery obstruction plus sympathectomy. That ligation of the femoral artery per se does not produce a flat postarterial occlusion blood flow curve is demonstrated by the third sympathectomized patient studied.

The hemodynamic status of arteriosclerotic involvement in the toe differs from that in the foot. The foot is rich in shunts and anastomoses. The toe is supplied by terminal arterial loops. When the arteries of the toe are diseased, hyperemic procedures directed to the foot and toe would be ineffective in producing an increase in toe flow (Landowne-Katz phenomenon), but instead would result in a decrease because of the shunting of blood proximal to the obstruction. The proper state of affairs would only be revealed by the toe plethysmographic blood flow method.

A study of the variations of resting flow measurements revealed the most consistent values in the gangrenous patients. The control subjects showed the most fluctuation, and the subjects with absent pulses were intermediate.

The recent excellent work of Scheinberg, Dennis, Robertson, and Stead[11] has demonstrated that five-minute arterial occlusion produces up to 40 per cent of maximal blood flow. This method, whereas it does not produce maximal flow, has served in our patients to differentiate the normal, intermediate, and gangrenous subjects.

CONCLUSIONS

1. Arterial occlusion technique is a suitable procedure for demonstrating a state of vascular insufficiency in the foot or toe. The blood flow values obtained by this method correlate well with the clinical findings and agree with the work of previous investigators. A summary of previous work has been tabulated.

2. Blood flow following arterial occlusion technique is superior to resting flow in the estimation of vascular insufficiency.

3. After arterial occlusion some patients having impalpable peripheral pulses demonstrated flow rates which overlapped into the lower range of normal. Gangrenous patients showed no overlap.

4. This technique showed some increase in blood flow to the foot in subjects with gangrene of the toes. A case of decrease in blood flow to the toe following arterial thrombosis is presented. The possibility of shunting of blood proximal to the vascular obstruction, with resultant decrease of blood to the toes, is discussed.

5. The physiologic hemodynamic difference between arteriosclerosis and thromboangiitis obliterans is discussed.

6. The Landowne-Katz effect (flat postarterial occlusion curve) is discussed, and its application in two cases of obstruction of the abdominal aorta and femoral artery is presented.

7. The value of toe-flow studies in arteriosclerosis obliterans is emphasized.

8. The variation of resting blood flow in normal, intermediate, and gangrenous groups is presented.

The authors are indebted to Doctors O. Leonard Huddleston, Phoebus Berman, and Charles Johnston for their cooperation in this study.

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A METHOD FOR THE PERCUTANEOUS INTRODUCTION OF VENOUS CATHETERS

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THE introduction of a venous catheter into an arm vein has led to an intensive investigation of circulation and respiration in congenital cardiac disease as well as in acquired cardiac and pulmonary disease.

The catheter is introduced by most investigators through a venesection. In principle the introduction can be accomplished percutaneously through a hollow needle, but in practice the large caliber of the needle which must necessarily be used makes this procedure inconvenient. Since venesection also has disadvantages, a method was sought which would circumvent the difficulties encountered in percutaneous introduction.

The instrument devised consists essentially of a hollow metal tube, split in four parts, which after being introduced in a folded form, permits the passage of the catheter. The instrument is composed of three separate pieces (Fig. 1):

I. The inner piece is a sharp needle of medium caliber with an ordinary tip. The small central portion of the needle is joined to the tip by an overlapping edge.

II. The outer piece of the instrument is formed by a hollow tube of sufficient width for passage of the catheter. The first portion of this tube is split into four parts. These parts can be compressed together to fit snugly under the edge of the inner needle. When pieces I and II are assembled, their outer surfaces should be quite smooth. If the outer piece is then retired a short distance, the four parts of the split tube escape from the edge of the inner needle and, by their own elasticity, curve slightly to the outside. The inner needle can then be retired and the catheter introduced through the outer tube, left in situ. This maneuver was found to be efficient outside the body, but when the instrument was inserted into a vein it was discovered that the four parts of the outer tube did not spread sufficiently for withdrawal of the inner needle. Obviously they were held together by the elasticity of the skin and the vein, and were caught on the edge of the inner needle when it was moved outward.

III. Therefore, a third piece was found necessary. A moving hollow tube was fitted on the small middle portion of the inner needle. Before insertion of the needle this is moved upward to the end piece. After the needle is introduced into

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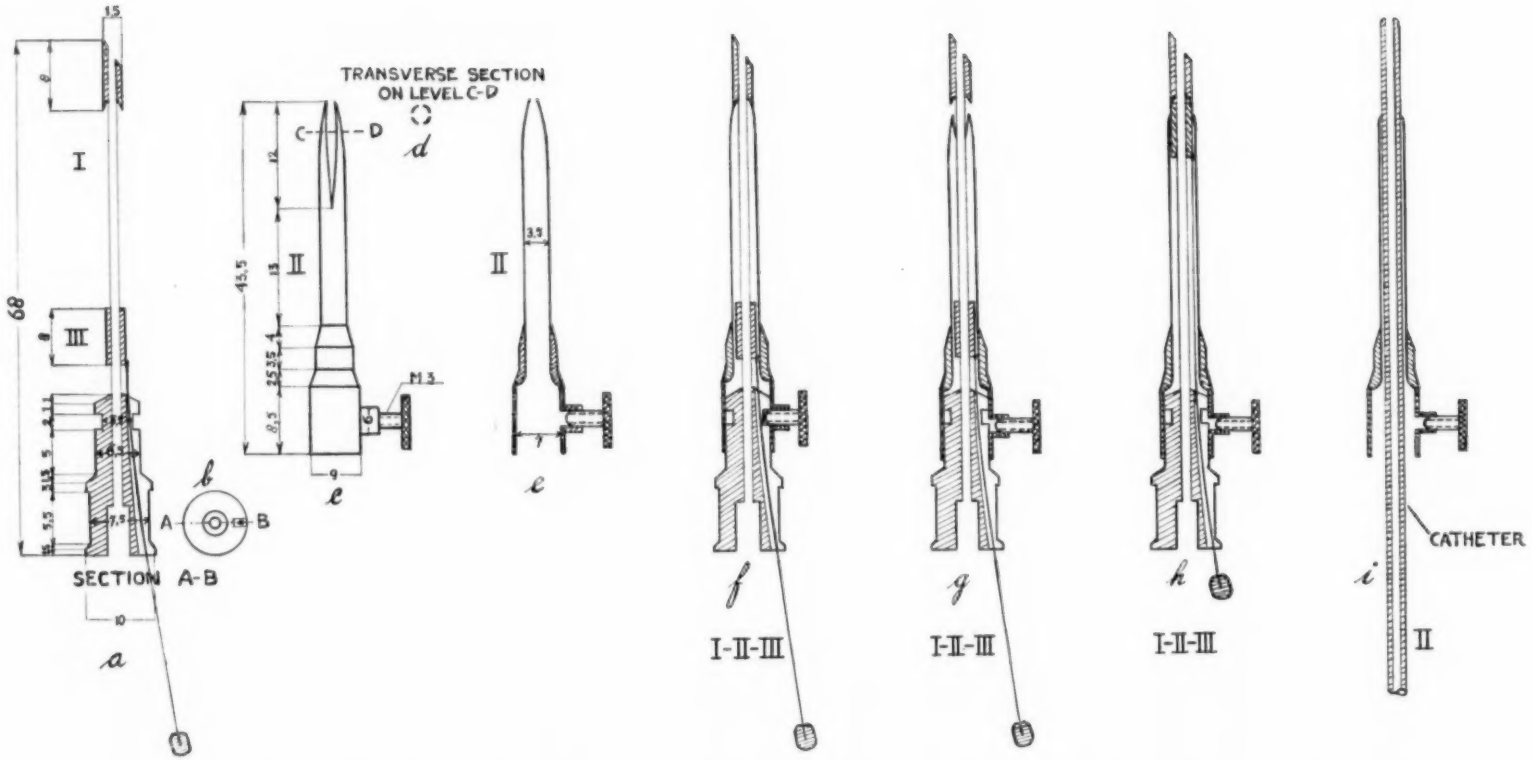

Fig. 1.—Instruments for introduction of venous catheters. *a*: Longitudinal section through inner needle (piece I) with the small, moving hollow tube (piece III). *b*: Transverse section of the inner needle (piece I) at the level of the end piece. *c*: Longitudinal view of outer hollow tube (piece II) showing splitting at the top. *d*: Transverse section of the outer hollow tube (piece II) at the level C-D of the preceding drawing (*c*) also showing the splitting of the top of the tube in four parts. *e*: Transverse section of the outer hollow tube (piece II). *f*: Assemblage of the three parts of the instrument ready for introduction into the vein. Pieces I and II are fixed together by the screw. *g*: Second position of the instrument after introduction into the vein. The screw has been moved back, loosening piece I from piece II. (Piece II has been retired a few millimeters, thereby freeing the split top from the overlapping edge of the inner needle.) *h*: The split parts of the hollow tube (II) have been forced outward, by the upward movement of the small moving tube (III), against the overlapping edge of the inner needle. The inner needle (I) and the moving tube (III) can be retired leaving the outer tube in the vein. *i*: The catheter is now introduced through the outer hollow tube (II) into the vein; the outer tube can be left in situ, or can be retired, leaving only the catheter in the vein.

the vein and the outer tube freed from the edge of the inner needle, the middle tube is moved down to the position where it fits into the inner edge and forces outward the four parts of the outer tube. The retirement of the inner needle presents no difficulties and the catheter can be introduced through the outer hollow tube.

Some further features may be mentioned. The outer tube (II) is reinforced at the end and is equipped with a screw at this point which makes it possible to fix pieces I and II together during the introduction of the instrument into the vein. After insertion of the instrument the screw is loosened and outer piece II is retired some millimeters, which frees the split portion from the inner needle. The moving hollow tube (III) is fitted with a steel wire which runs through a groove in the end piece of the inner needle and projects outside the instrument. This makes it possible to move the hollow tube (III) down against the edge of the inner needle, thereby forcing out the split portion of outer tube II. After the inner needle (I) and the moving tube (III) are withdrawn, the catheter is introduced. The procedure is facilitated if the instrument is pushed well into the vein at the beginning. Otherwise some friction between the catheter and the outer tube may occur. In this event the outer tube can be withdrawn from the vein following the introduction of the catheter, leaving only the catheter in the vein.

Venous catheters have been introduced by this method on several occasions with success. It is obvious that a vein of sufficient caliber leading to the inner surface of the arm should be present. In our experience, when such a vein was absent the venesection also was performed with great difficulties; sometimes we have been obliged to use the other arm or even to open a deep brachial vein in the upper arm.

This method is of definite advantage in that the vein is not tied off and often stays open so that it can be used a second time if necessary. The description of this instrument may make its use seem complicated. In reality, however, the procedure is very simple and after the needle has been introduced into the vein the further manipulations do not present any difficulties.

VISUALIZATION OF THE CORONARY CIRCULATION DURING ANGIOCARDIOGRAPHY

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NEW YORK, N. Y.

IN THE course of routine angiocardiography in man, we occasionally have been able to identify the coronary arteries and coronary sinus. It is the purpose of this report to reproduce selected roentgenograms which demonstrate these vessels and to comment briefly upon the circumstances under which they were seen.

The coronary vessels have been visualized radiographically in the living animal on several previous occasions. In 1933, Rousthöi[1] injected Thorotrast into the aorta of living rabbits through a ureteral catheter inserted into the carotid artery. In his roentgenograms both main coronary arteries were clearly shown. During investigations of the fetal circulation of sheep, Barclay, Barcroft, Barron, and Franklin[2] also demonstrated the coronary arteries roentgenographically. In a moribund fetus, Thorotrast was injected in a retrograde fashion through the femoral artery, outlining the aorta and coronary arteries. Grossman,[3] in 1945, using a technique similar to that of Rousthöi, but utilizing 70 per cent Diodrast as the contrast medium, succeeded in outlining the coronary arteries of living dogs. An attempt to demonstrate the coronary arteries of man was made, unsuccessfully, by Radner[4] in 1945. He injected Thorotrast by direct needle puncture of the aorta through the sternum. Radner[5] recently described a technique of injecting Diodrast solution directly into the human aorta through a ureteral catheter introduced through the brachial artery. With this method, Crafoord and his co-workers[6] have succeeded in outlining the coronary arteries.

Shortly after the first paper by Robb and Steinberg,[7] angiocardiography was undertaken in this department.[8] Details of the present method and a summary of the earlier work are available elsewhere.[9,10] In brief, 70 per cent Diodrast is injected rapidly through a trocar inserted into an antecubital vein. In infants the saphenous vein is frequently used. A series of twelve ten- by twelve-inch roentgenograms are made in rapid succession by means of an especially designed upright casette-changer. Exposures are made at a maximum rate of two per second. The R wave of the action current of the heart in Lead CF_3 or CF_4 is amplified to activate a synchronizing mechanism so that each exposure is predetermined in regard to the number of heart beats after injection and to the

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phase of the cardiac cycle. In children, because of the rapid rates encountered, and associated technical limitations, the majority of exposures are taken midway in the cardiac cycle (about 0.2 to 0.3 second after the peak of the R wave). Usually, roentgenograms are made at alternate beats. In adults, more freedom is permitted in the timing of the films, and delay relays are used to make the exposures later in the cardiac cycle. The electrocardiogram is recorded with a direct-writing instrument.* A feed-back voltage from the primary winding of the high-voltage (x-ray) transformer registers where each exposure occurs. This electrocardiographic record is also used to determine, for each film, the approximate elapsed time after the beginning of the Diodrast injection. Ether anesthesia, usually preceded by rectal Avertin, has been found necessary for best results in infants and children. Exposures are usually made in one-sixtieth of a second.

THE CORONARY ARTERIES

One or more of the coronary arteries has been visualized in at least ten of approximately 1,200 angiocardiographic examinations made during the past eight years. Up to now, we have seen the coronary arteries chiefly in children, probably because the aorta and its branches are particularly well visualized in children, as compared with adults. This is attributable, in part, to the better contrast in the films made in young subjects. We have not been able to ascertain what other factors might operate to prevent visualization of the coronary arteries. We cannot explain why they are seen in only a small percentage of cases, since it is inconceivable that Diodrast-containing blood should fail to enter the coronary system during the period of visualization of the aorta. Furthermore, the concentration of the contrast substance does not appear to play a role, because the density of the opacified aorta is no greater in the present cases than in most of the others. In many films the coronary arteries are obscured by Diodrast in the pulmonary vessels, but in others this factor is not present.

The right main coronary artery has been clearly identified several times. The left has been identified with reasonable certainty only once. That occurred in a case of dextroposition of the aorta (tetralogy of Fallot) in which the aorta was particularly opaque because of a marked degree of overriding. A possible explanation of these phenomena is as follows: The patients are almost always in the left anterior oblique or anteroposterior position, since these positions have been found by experience to give the most information. The coronary arteries normally fill with contrast substance at the same time as the aorta. However, the left auricle, and sometimes the left ventricle, is visualized on the same films. Consequently, the left coronary arteries are obscured by the underlying chambers. On the other hand, the chambers of the right side are usually empty of Diodrast at this time, and the right coronary artery is not obscured. In order for the left coronary artery to be clearly seen, it would be necessary for the aorta to fill independently of the left ventricle and left auricle. This condition is fulfilled in any congenital lesion in which the aorta arises, either in whole or part, from the right ventricle, such as occurs most commonly in the tetralogy of Fallot and its variants (see Case 5).

*Cardiotron, made by the Electro-physical Laboratories, New York City.

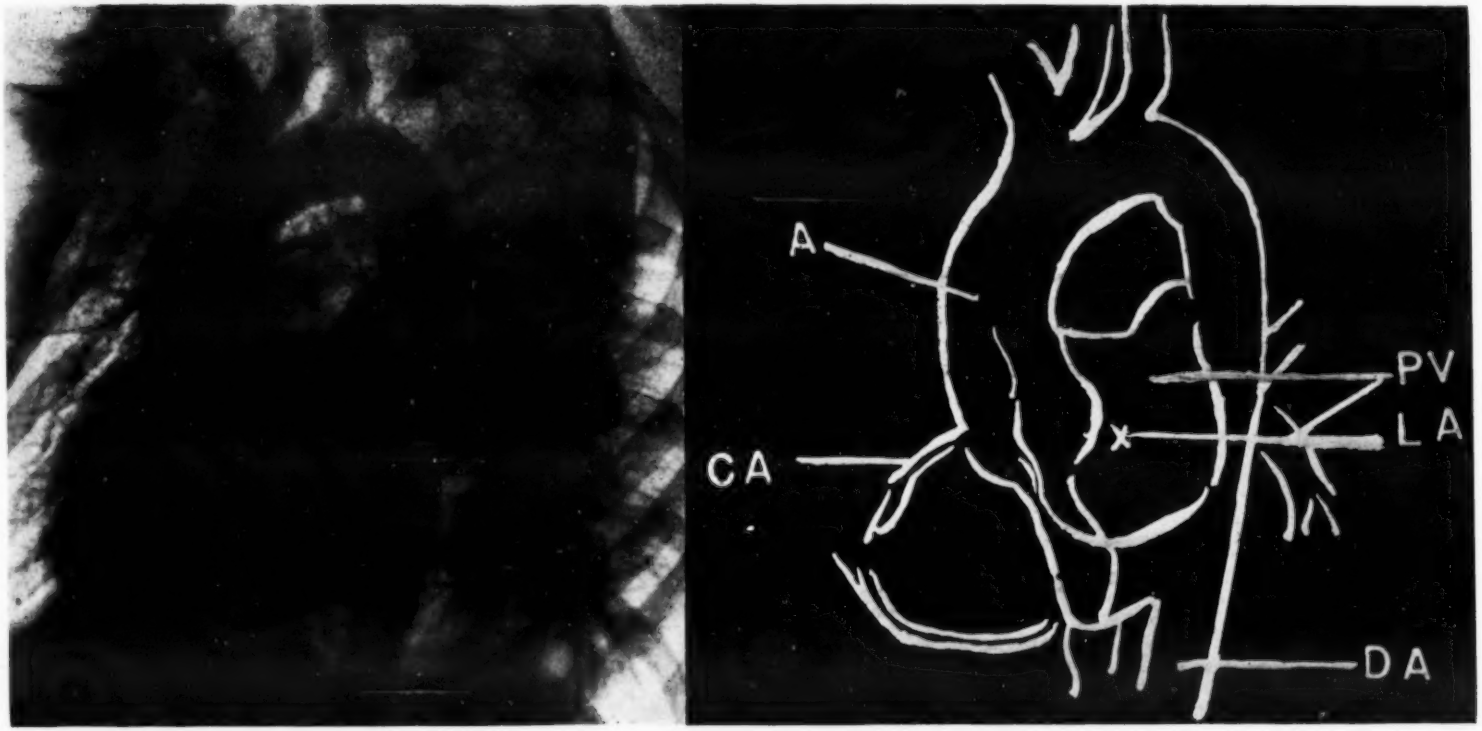

Fig. 1.—Angiocardiogram in Case 1. The right coronary artery is seen arising from the sinus of Valsalva. The pulmonary veins still contain Diodrast. *CA*, right coronary artery; *A*, aorta; *PV*, pulmonary vein; *DA*, descending aorta; *LA*, left auricle.

When it is filled with Diodrast, the right main coronary artery is not difficult to identify. It is a narrow vessel, arising from the upper part of a bulge at the origin of the aorta representing the sinus of Valsalva. It courses downward and to the right, curving backward and reversing its direction as its caliber decreases. The apparent change in direction presumably occurs when it crosses the margo acutus to descend along the posterior auriculoventricular sulcus.[11] Small branches of the vessel can often be seen in the films.

The identity of the left anterior descending artery is more difficult to establish. In general, similar criteria are used: these include the visualization of a vessel which arises from the region of the sinus of Valsalva simultaneously with the aorta, is of the proper size, and courses in the proper direction.

Fig. 2.—Angiocardiogram in Case 2. Arrow indicates the right main coronary artery.

CASE REPORTS

CASE 1 (Fig. 1, Table I).—E. D. was a 7-year-old girl with the clinical diagnosis of patent ductus arteriosus. The angiocardiographic diagnosis was consistent with patent ductus arteriosus. The anesthetic agents were Avertin and ether. The x-ray position was the left anterior oblique. The right coronary artery was first seen in the film taken during the seventh heart beat after injection, and continued to be filled with Diodrast for 2.6 seconds. All exposures were made 0.20 second after the R wave, except No. 6, which occurred 0.12 second after it.

TABLE I. TABULAR DATA ON ALL CASES

CASE NUMBER	FILM NUMBER	BEATS AFTER BEGINNING OF INJECTION*	DELAY AFTER R WAVE	R-R INTERVAL	HEART RATE	SECONDS AFTER BEGINNING OF INJECTION*	REMARKS
1. (E. D.)	4	7	0.20	0.44	136	4.4	Right coronary artery visualized in all films
	5	9	0.20	0.44	136	5.2	
	6	11	0.12	0.44	136	6.0	
	8	13	0.20	0.44	136	7.0	
2. (B. S.)	4	7	0.20	0.44	136	3.2	Right coronary artery visualized in all films
	5	9	0.20	0.44	136	4.0	
	6	11	0.20	0.44	136	4.9	
3,*A*. (L. C.)	6	7	0.20	0.52	117	3.1	Right coronary artery visualized in all films
	8	9	0.20	0.52	117	4.0	
	9	11	0.20	0.52	117	5.1	
3,*B*. (L. C.)	9	9	0.30	0.56	107	4.8	Right coronary artery visualized in both films
	10	11	0.30	0.62	97	6.0	
4. (I. F.)	7	13	0.20	0.36	167	4.9	Right coronary artery visualized in all films
	8	15	0.20	0.36	167	5.6	
	9	17	0.20	0.36	167	6.4	
5. (P. M.)	2	3	0.06	0.32	187	1.0	Both coronary arteries seen, the left more clearly, in all films
	3	5	0.04	0.32	187	1.6	
	4	7	0.06	0.32	187	2.4	
6. (J. G.)	4	4	0.18	0.60	100	2.5	Coronary sinus seen
	5	5	0.28	0.58	103	3.2	Coronary sinus *not* seen
	6	6	0.18	0.58	103	3.7	Coronary sinus again visualized
7. (R. S.)	3	5	0.20	0.54	111	2.6	Coronary sinus seen in all films
	4	7	0.20	0.54	111	3.7	

***In this series of experiments the beginning of the injection was not timed accurately. It has been assumed for these observations that the injection began coincident with the R wave which preceded the one activating the exposure mechanism.**

CASE 2 (Fig. 2, Table I).—B. S., a 3-year-old girl, had a final clinical diagnosis of normal heart with a functional, apical systolic murmur and an angiocardiographic diagnosis of normal angiocardiogram. The anesthetic agents were Avertin and ether. The x-ray position was the left anterior oblique. The right main coronary artery was first seen during the seventh beat (3.2 seconds) after injection. At this time the left auricle, the left ventricle, and the aorta with its branches were filled. All films were taken 0.20 second after the R wave, on the downstroke of the T wave.

Fig. 3.—Case 3, *A*. The right coronary artery is seen arising from the sinus of Valsalva (arrow). This roentgenogram was made 0.2 second after the peak of the R wave and is nine heart beats after the beginning of injection.

CASE 3 (Fig. 3).—L. C., a 6-year-old girl, had a final clinical diagnosis of normal heart with apical systolic murmur. The angiocardiographic diagnosis was normal angiocardiogram. The anesthetic agents were Avertin and ether. The x-ray position was the left anterior oblique. The procedure was carried out twice in succession, the difference being that the first series of films was made 0.20 second after the R wave, the second series 0.30 second after it (see Table I). In the first series (Case 3,*A*), the right coronary artery was visualized during the seventh, ninth, and eleventh heart beats (3.1, 4.0, and 5.1 seconds, respectively), after injection. On these films, the pulmonary artery is still faintly seen and the left auricle and ventricle are superimposed. The aorta and its branches are visible. In the seconds series (Case 3,*B*), the same vessel is seen during the ninth and eleventh heart beats (4.8 and 6.0 seconds) after injection.

CASE 4 (Fig. 4).—I. F., an 8-year-old girl, had a clinical diagnosis of patent ductus arteriosus. Angiocardiographic findings were compatible with patent ductus arteriosus. The anesthetic agents were Avertin and ether and the x-ray studies were done in the left lateral position. The right main coronary artery was seen during the thirteenth heart beat after injection, an elapsed time of 4.9 seconds.

CASE 5 (Fig. 5).—P. M. was a 2-year-old girl whose clinical diagnosis was tetralogy of Fallot. The angiocardiographic diagnosis was the same. Avertin and ether were used for anesthesia and the x-ray position was the left anterior oblique. The aorta and the pulmonary arteries filled simultaneously from the right ventricle. The left anterior descending artery and a portion of the right coronary artery filled with Diodrast and are faintly visible on the films taken during the third, fifth, and seventh heart beats, 1.0 to 2.4 seconds after injection. The identification of these structures is not as certain as in the other patients.

Fig. 4.—Case 4. The appearance of the right coronary artery in a lateral view.

DISCUSSION

In the first three patients, whose circulation is not grossly abnormal, the right main coronary artery is seen to fill with contrast substance during the period from the seventh to the eleventh heart beats after injection. The arm-to-coronary artery circulation time in these children varies from 3.0 to 4.8 seconds, and the time during which the artery remains visualized varies from 1.2 to 2.6

seconds. As mentioned previously, these figures are not exact as related to the beginning of injection. In Case 4, which differs from the first three in having a more rapid heart rate (167 per minute), the vessel is not seen until the thirteenth beat after injection, although the arm-to-coronary artery circulation time is the same.

In Case 5, in which the aorta fills directly from the right ventricle, the coronary arteries are visible at the third beat after injection, only about one second in actual time.

Fig. 5.—Tetralogy of Fallot (Case 5). The aorta fills with Diodrast simultaneously with the right side of the heart. The right auricle and ventricle are superimposed. The pulmonary artery is not identified in this film. The fine line along the left ventricular border probably represents the left anterior descending coronary artery. A fine twig of a terminal branch of the right coronary artery is also seen.

It is also of interest that the coronary arteries are filled with contrast substance in different phases of the cycle: in early systole in Case 5; in maximum systole in Cases 1, 2, 3,*A*, and 4; and in early diastole in Case 3,*B*. Unfortunately, none of these films were exposed at the point of maximum diastole (immediately before the R wave) so that no statement can be made relative to that part of the cycle.

THE CORONARY SINUS

An opacified structure which we have taken to be the coronary sinus has been clearly visualized on two occasions during angiocardiography in adults. In each

Fig. 6.—The superior vena cava and pulmonary artery are clearly visible (Case 6). The right auricle and right ventricle are superimposed. The coronary sinus is seen emptying into the region of the right auricle.

instance it filled with Diodrast within a few seconds of the injection, simultaneously with the right auricle and ventricle, leaving no doubt that the contrast substance entered in reflux fashion from the right auricle. Possibly the pressure

in the right auricle at the end of the injection of about 50 c.c. of Diodrast is higher than that in the coronary sinus. On the other hand, the infrequency of the visualization suggests that other factors, some possibly anatomical, operate.

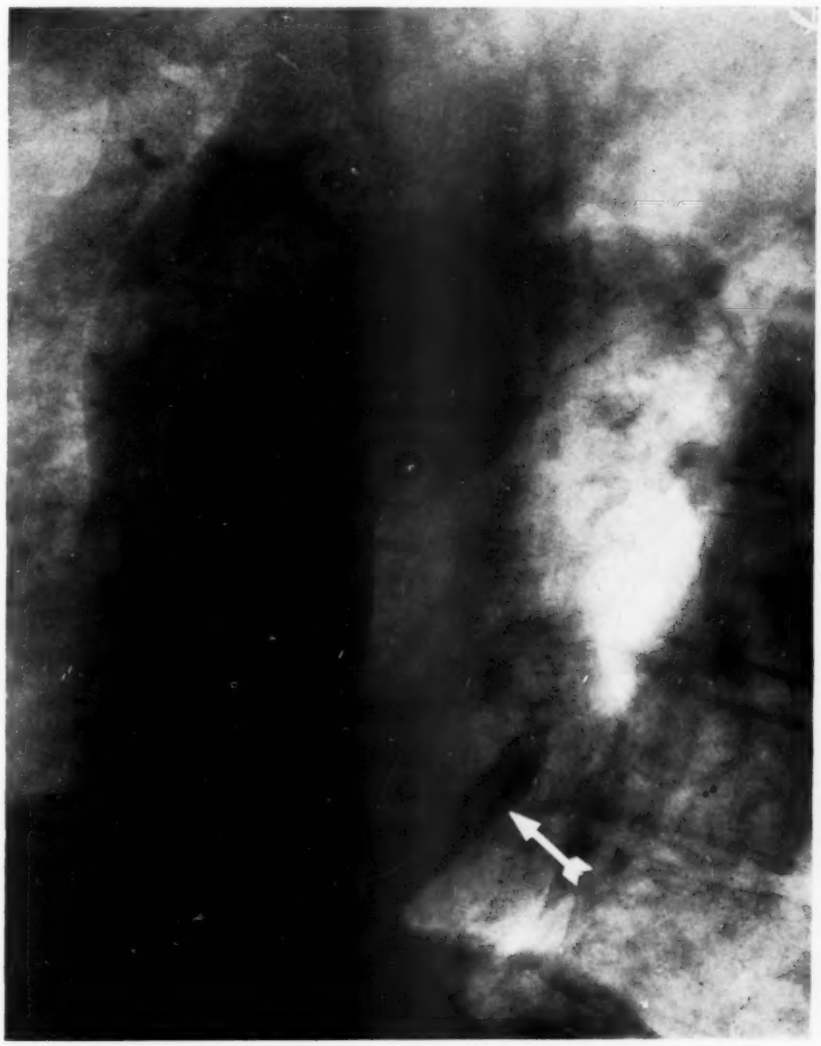

Fig. 7.—The coronary sinus is visualized as a broad projection from the right side of the heart (Case 7).

The coronary sinus in our films is seen as a straight, wide vessel arising from the lower border of the right auricle and tapering slightly as it courses upward and backward for a distance of 4.0 or 5.0 centimeters. The Diodrast has not entered far enough or in sufficient concentration to cause any of its branches to become opacified.

CASE REPORTS

CASE 6 (Fig. 6).—J. G. was a 53-year-old man whose clinical diagnosis was atypical coarctation of the aorta and whose angiocardiographic study was unsatisfactory. The x-ray position was the left anterior oblique. The coronary sinus was seen in the fourth and sixth films, but not in the fifth (see Table I). The only difference between these films is that the fifth was taken later in the cycle, nearer maximum systole. Initial visualization occurred 2.5 seconds after the injection while the right side of the heart was filled with Diodrast.

CASE 7 (Fig. 7).—R. S. was a 49-year-old woman whose clinical diagnosis was aneurysm of the aorta. The angiocardiographic diagnosis was dissecting aneurysm of the aorta. The x-ray studies were done in the left anterior oblique position. The coronary sinus filled with Diodrast during the fifth and seventh heart beats (2.6 and 3.7 seconds) after injection. Simultaneously, the right side of the heart was seen.

SUMMARY

The coronary arteries and the coronary sinus may occasionally be identified in the films taken during routine angiocardiography in man. The arteries are seen mainly in children, in whom the aorta and its branches are usually more clearly outlined. In adults, the coronary sinus is sometimes filled in retrograde fashion from the right auricle.

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THE ELECTROCARDIOGRAM FOLLOWING ANASTOMOSIS OF CAROTID ARTERY TO CORONARY SINUS

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THIS report concerns electrocardiographic changes observed in experiments on dogs after transplantation of the peripheral end of the common carotid artery into the coronary sinus. The work was done in conjunction with the study on revascularization of the heart by Beck, Stanton, Batiuchok, and Leiter.[1]

THE PROCEDURE ON DOGS

The coronary sinus was ligated with silk a few millimeters from its ostium. The ligation was either partial or complete. For partial ligation the ligature was placed around the sinus and tied on a stilette. For complete ligation, double silk ligatures were tied around the sinus.

One to three weeks later the left common carotid artery was transected below its bifurcation and brought into the chest. Complete ligation of the sinus was done if the sinus had been partially ligated. Anastomosis was made between the carotid artery and the coronary sinus distal to the point of ligation.

Two weeks following this procedure the descending ramus of the left coronary artery was dissected. This artery was completely ligated at its origin in one step.

The technique of these operations is described in the original communication.[1]

Electrocardiograms were obtained before and after each of the procedures.

EFFECT OF SINUS LIGATION

Immediately following partial ligation of the sinus there is a slowing of the heart rate. The rate returns to normal within a few minutes. In the following one to ten days there is an increase in rate. In one dog there was a subsequent sinus tachycardia (220 beats per minute). In all cases the T wave was increased in height with variable elevation of the RS-T segments and a consistent elevation and peaking of the T wave in Lead V_4.

Following complete ligation of the sinus, changes were similar (Fig. 1). There was an increase in the heart rate (average increase in rate of twenty to forty beats per minute). There was occasional transient elevation of the RS-T segments in Leads II and III, and occasional transient inversion of T_2 and T_3. The changes in the RS-T segment and T wave in V_4 were more pronounced. In a few dogs there was an intermittent shifting from sinus to nodal rhythm. In one there was a 1:1 ventricular response alternating with a 2:1 auriculoventricular block. These changes suggest damage of the auriculoventricular node.

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The changes described agree closely with those reported by Gross, Silverman, and Master[2] following ligation of the coronary sinus. The changes in the T waves are believed primarily due to alteration in repolarization. The transient changes in the RS-T segments and the occasional inversion of T_2 and T_3 may be due to venous congestion and transient myocardial ischemia. Gregg and Dewald[3] have shown that the oxygen saturation of blood in the coronary arteries is greatly reduced by ligation of the coronary sinus.

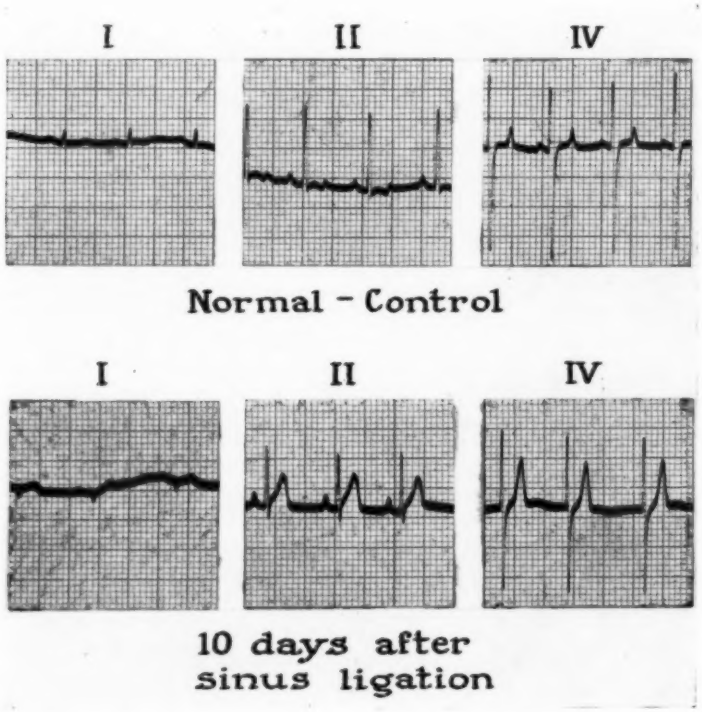


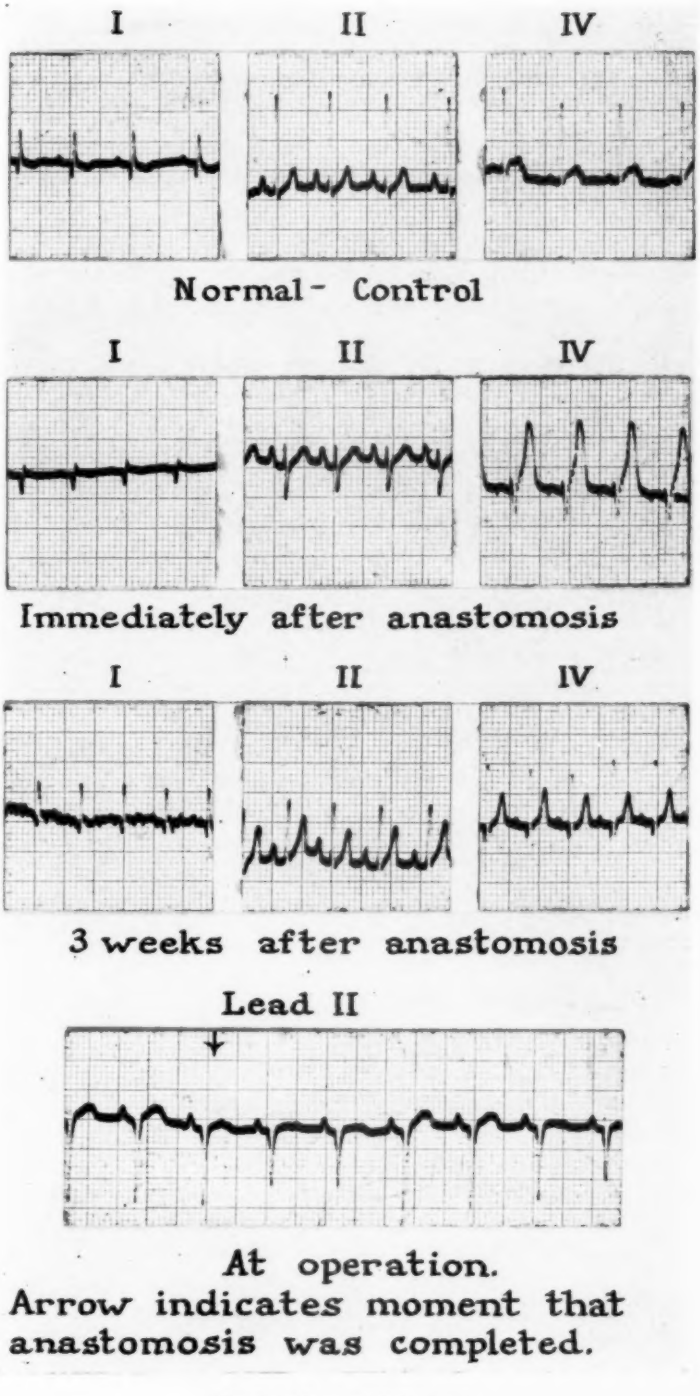
Fig. 1.—Records made preoperatively and ten days after complete ligation of coronary sinus. Note the large T waves after sinus ligation. IV refers to Lead V_4.

EFFECT OF CAROTID ANASTOMOSIS TO THE LIGATED CORONARY SINUS

Immediate Effects (Fig. 2).—All tracings taken at the time of operation show changes in the QRS complex. There is a cyclic variation in voltage believed due to mechanical respiration. In some instances the P waves are increased in amplitude; in most there is a delayed intraventricular conduction time with a

Fig. 2.—Effect of anastomosis of carotid artery to coronary sinus. In the immediate postoperative record note the Q_1, the deep S_2 and S_4, and the greatly elevated T wave in V_4. In the record taken three weeks later note the similarity to the normal record except for the large T waves in Leads II and V_4 (IV). IV refers to Lead V_4.

The lowest record was taken at the operating table at the moment the anastomosis was completed and the bulldog clamp was removed from the carotid artery. The dog was on its left side. Note the normal sinus rhythm, the cyclic variation in potential, and the lack of immediate change following removal of the clamp.



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prolonged QRS interval; and in some there is a transient bundle branch block during operation. All T waves are prolonged and may be biphasic. In no case was there any immediate change noted in the tracing at the moment the anastomosis was completed and arterial blood allowed to course through the coronary sinus.

The changes in the QRS complex during operation involve factors of position, temperature, and mechanical trauma. The cyclic variation in potential follows the rate of mechanical respiration. The delayed conduction time and occasional transient bundle branch block are probably due to the extensive manipulation with transient myocardial damage. The proximity of the auriculoventricular node to the site of anastomosis probably is also a factor in the disturbances of conduction.

Delayed Effects.—Tracings taken twenty-four hours to four months following the anastomosis show little change from normal except transient disturbances of the RS-T segments and the T waves. These changes are similar to those produced by sinus ligation alone.

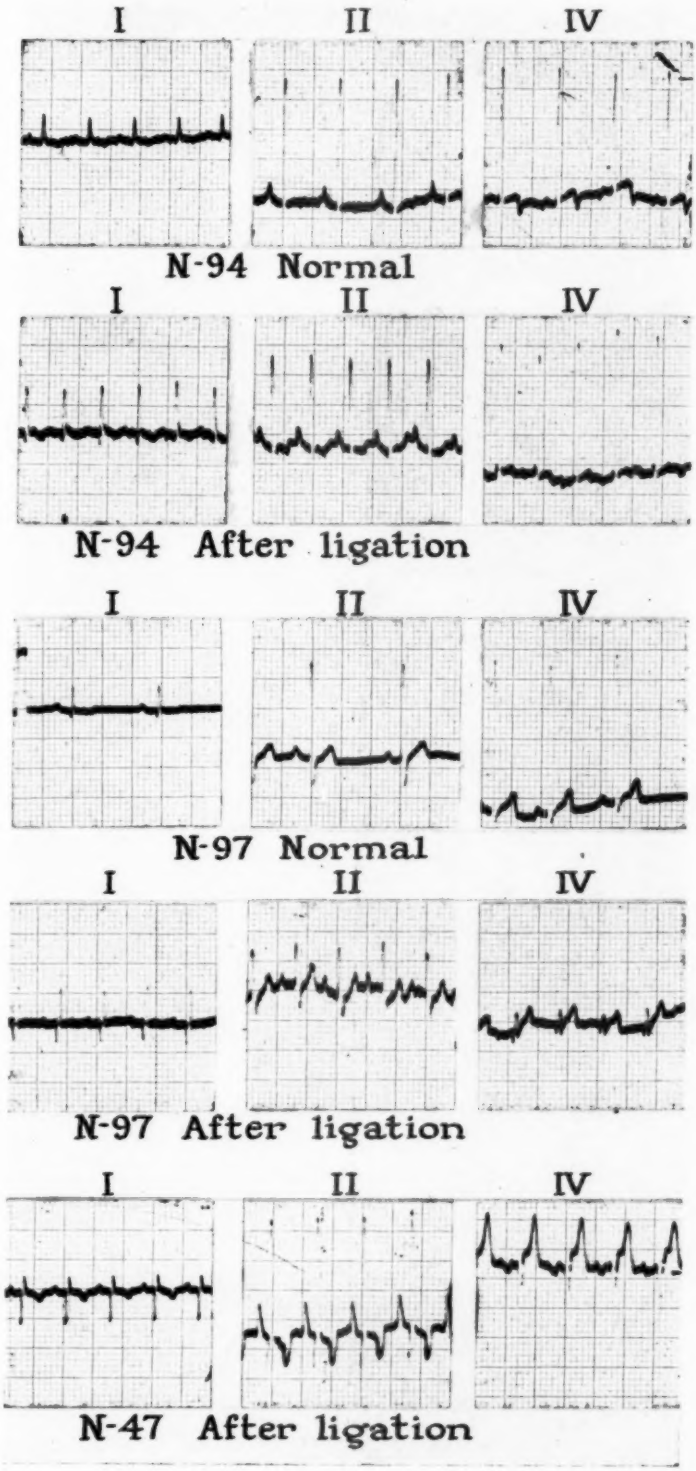
EFFECT OF LIGATION OF THE DESCENDING RAMUS OF THE LEFT CORONARY ARTERY

A. *In Dogs Later Shown to Have Thrombosis of the Carotid Anastomosis.*—In a group of ten consecutive dogs later shown to have thrombosis of the transplanted artery, seven died immediately (less than forty-five minutes) following ligation of the descending coronary artery. Three dogs with thrombosed grafts survived ligation. Serial tracings were obtained after ligation. In all three there was conclusive evidence of anterior infarction (Fig. 3, N-47). There was a deep Q_1, development of a Q_2 and Q_3, a persistent QRS complex and elevation of the RS-T segment in Lead V_4. There was inversion of T_2 and T_3. Anterior apical infarcts were present in the sacrificed specimens.

B. *In Dogs Shown to Have Patent Carotid-Coronary Sinus Anastomosis.*—In ten consecutive patent anastomoses, all ten animals survived the immediate postoperative period. One dog died eight days later; another died thirteen days later; and the remainder were sacrificed in from fifteen days to four months after ligation.

No tracing was obtained of the dog which died in thirteen days. Serial records were obtained on the other nine dogs. The dog which died in eight days developed a ventricular tachycardia on the sixth day and showed elevation of the RS-T segments in Leads II and III with inversion of T_2 and T_3, and development of a Q wave in V_4. The post-mortem specimen contained a 1.0-cm. infarction in the anterior portion of the left ventricle and the interventricular septum. Four sets of tracings showed variable changes in the RS-T segments, inversion of T_2 and T_3, and a small Q wave in V_4. Two of these dogs had infarctions of less than 0.5 cm. when sacrificed; the other two had diffuse interstitial fibrosis with no specific infarction (Fig. 3, N-97). The remaining sets of records were within normal limits and the specimens showed no signs of infarction (Fig. 3, N-94).

Fig. 3.—Effect of ligation of the descending ramus of the left coronary artery in dogs with carotid-coronary sinus anastomosis. N-94 had no infarct; N-97 had a small infarct in the anterior papillary muscle; both had patent anastomoses. N-47 had a large anterior apical infarct; the anastomosis was thrombosed. IV refers to Lead V_4.



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SUMMARY

This is a report of the electrocardiographic changes noted after coronary sinus ligation, anastomosis of the carotid artery to the coronary sinus, and subsequent ligation of the descending ramus of the left coronary artery.

The changes following ligation of the coronary sinus are similar to those noted by Gross and his colleagues.[2] These changes are transient and reflect disturbance of the myocardium due to mechanical trauma, and perhaps a transient ischemia due to venous congestion.

Records taken at the time of anastomosis of the carotid artery to the coronary sinus show extensive changes in the QRS complex, the T waves, and the conductive mechanism. These changes are transient and reflect position change, temperature change, mechanical trauma, and myocardial injury. No change was noted at the moment of release of arterial blood into the sinus.

Serial records following ligation of the descending ramus of the left coronary artery in dogs with patent anastomosis showed no sign of infarction in four of nine subjects; four showed suggestive signs of infarction; one showed definite signs of infarction. All survived the immediate postoperative period. In all cases of ligation in which the anastomosis was thrombosed there were signs of myocardial infarction.

This evidence suggests that an arterial anastomosis into the coronary sinus will frequently protect the dog's heart against one-step ligation of the anterior descending ramus of the left coronary artery.

The author expresses his appreciation to Dr. Harold Feil for his review of the electrocardiograms of this study.

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Clinical Reports

ACUTE MYOCARDITIS

Report of a Case With Observations on the Etiologic Factor

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WHENEVER acute myocarditis is diagnosed clinically, an etiologic agent can seldom be identified. In the absence of rheumatic fever, diphtheria, or other significant infection, the term "isolated" or "idiopathic" (Fiedler's) myocarditis is used. The following instance of probable acute myocarditis in a young man who recovered is being reported because there was a clue as to cause.

CASE REPORT

A 29-year-old laborer was admitted to the hospital on April 7, 1947, because of congestive heart failure.

He had been well until a week prior to entry when he developed malaise and a nonproductive cough. There had been no coryza, pharyngitis, or joint symptoms. Six days prior to admission exertional dyspnea appeared and became progressively more severe. A dull, aching pain associated with an enlarging mass in the midepigastrium was noted.

The patient continued to work until noon of the day prior to admission when he returned home because of severe breathlessness and extreme weakness. He retired but was unable to breathe when lying flat. Paroxysmal coughing produced frothy pink sputum containing occasional clots of bright red blood. Cyanosis of the lips and swelling of the eyelids developed over a period of four to six hours. There had been no chills or fever. In the early morning of the day of admission he was seen by a physician who administered digitalis and penicillin. No sulfonamides were given. He was admitted to the hospital twelve hours later.

Physical examination revealed a well-developed man who was cyanotic, dyspneic, orthopneic, and was coughing up frothy pink sputum. The neck veins were distended. There was slight edema of the face and eyelids. The heart was enlarged to the right and to the left. The point of maximal impulse was 3 cm. to the left of the midclavicular line. The heart sounds were diminished in intensity. There was a protodiastolic gallop rhythm. No murmurs were heard. Both lung fields were filled with large and fine moist râles. The liver extended 5 cm. below the right costal margin and was tender to palpation. There was no ankle edema.

The temperature was 103° F., the pulse rate was 110, and the respiratory rate was 22. The blood pressure was 100/80. There was a pulsus alternans. The vital capacity was 1,800 cubic

From the Veterans Hospital and The Department of Medicine, University of Minnesota, Minneapolis, Minnesota.

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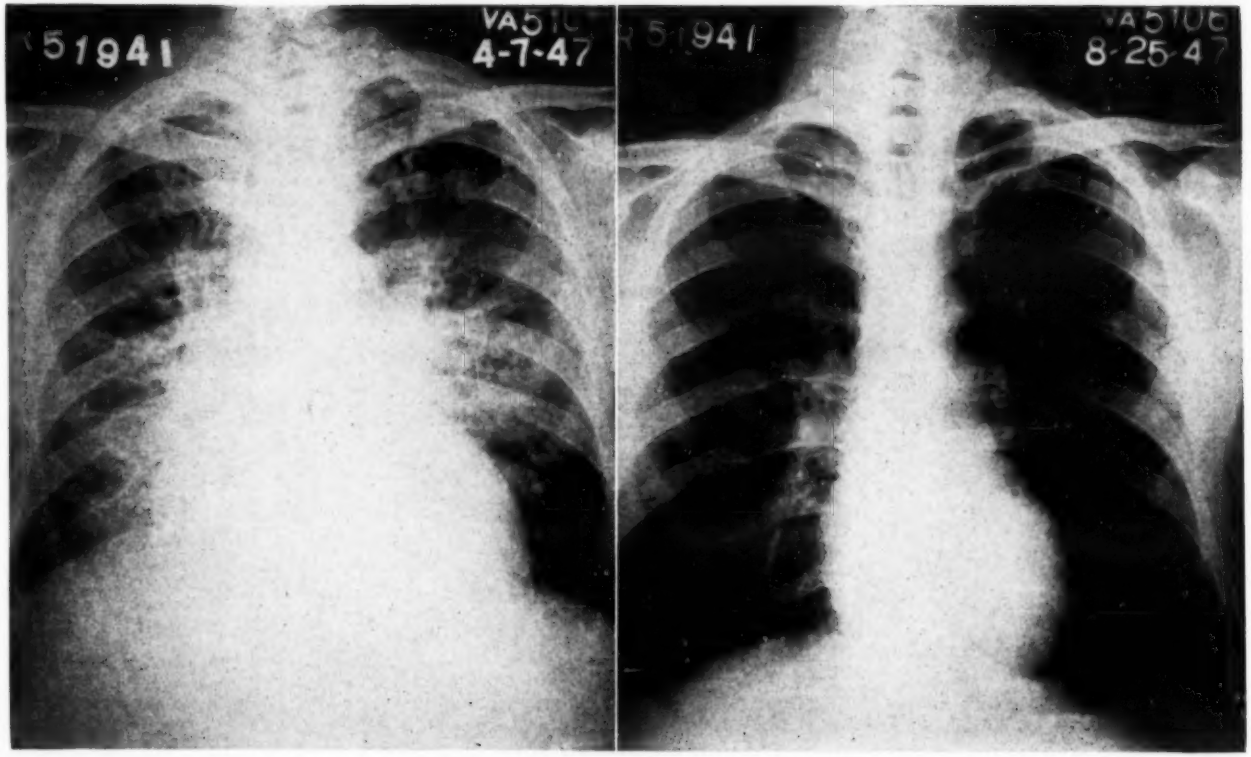

A B

Fig. 1.—Roentgenograms of the chest taken in the upright position at a focal distance of 6 feet. *A*, roentgenogram made on April 7, 1947, on day of admission to the hospital; *B*, roentgenogram made on Aug. 25, 1947, following discharge.

centimeters. The circulation time with sodium cyanide was 26 seconds. The venous pressure in the antecubital vein was 24.5 cm. of saline.

Examination of the blood revealed a hemoglobin of 14.9 grams and a white cell count of 9,850 per c. mm. with 63 per cent neutrophiles and 32 per cent lymphocytes. The erythrocyte sedimentation rate was 7 mm. per hour. The urine had a specific gravity of 1.025 and gave a faintly positive reaction for albumin. Culture of the blood yielded no growth. Sputum culture yielded a few colonies of a mixed growth of oral flora in which the predominate organism was hemolytic streptococcus.

Roentgen-ray examination of the chest showed marked pulmonary congestion and generalized enlargement of the cardiac silhouette (Fig. 1). The electrocardiogram showed low voltage of all QRS complexes in the limb leads with an isoelectric T_1 and an inverted T_2 and T_3. There was a low R wave in Lead CF_4 (Fig. 2).

The temperature twelve hours after admission rose to a maximum height of 104.6° F., after which it gradually fell, reaching normal on the sixth hospital day. The erythrocyte sedimentation rate rose to 49 mm. per hour on the fourth hospital day and remained around 36 mm. per hour until the eighth week of hospitalization when it fell to a normal value of 17 mm. per hour.

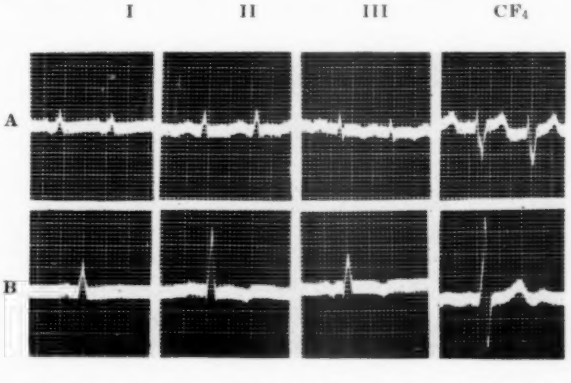

Fig. 2.—*A*, electrocardiogram made on April 7, 1947, on day of admission to the hospital. *B*, electrocardiogram made on Aug. 25, 1947, following discharge.

The patient was given the usual treatment for congestive heart failure. There was gradual improvement in the cardiac decompensation with decrease in the size of the heart over a four-week period. The protodiastolic gallop rhythm persisted for ten weeks. The electrocardiogram showed a persistent inversion of T_2 and T_3 (Fig. 2). The heart size as determined by roentgenogram was normal at this time although there was slight prominence in the region of the left ventricle (Fig. 1). The patient was discharged from the hospital eleven weeks after the onset of his illness. He was asymptomatic except for dyspnea on moderately severe exertion.

Special Studies.—Specimens of serum collected on the fourth (April 11) and fourteenth (April 21) day of the acute illness were tested simultaneously for the presence of influenza antibodies by the Medical Laboratories of the Minnesota Department of Health. The method employed in these studies was a modification of the technique described by Hirst.[3]

The acute serum collected on the fourth day of the acute illness showed inhibition of agglutination in a dilution of 1:8 for influenza A and 1:16 for influenza B. The corresponding values for the convalescent serum collected on the fourteenth day of the acute illness were 1:32 for influenza A and 1:16 for influenza B. This represents a four fold increase in the virus A antibodies, the virus B antibodies remaining the same.

DISCUSSION

The case reported here presented a typical picture of acute congestive heart failure, in a young man, due to an acute myocarditis of undetermined origin.

The working diagnosis was acute (Fiedler's) isolated myocarditis. Cardiac symptoms had been preceded by a mild respiratory illness which began on March 31, 1947. There was no evidence of tonsillitis, diphtheria, or rheumatic fever. Specimens of serum collected in the acute phase of the illness and ten days later in convalescence were tested simultaneously and showed a fourfold increase in the antibody titer against the influenza A virus. Such an increase is considered generally to be of diagnostic significance.

Myocarditis severe enough to provoke cardiac dysfunction occurs irregularly as a sequela to virus infections. Finland, Parker, Barnes, and Joliffe[2] in 1945 reviewed the literature on the occurrence of myocarditis following influenza and reported two instances of acute myocarditis in which the virus of influenza A was isolated from the lungs at necropsy. In a recently reported instance,[3] in which the patient died at the time of a mild epidemic of influenza A, the virus of influenza was mentioned as a possible cause of the diffuse myocarditis found at necropsy although no special studies for viruses were undertaken.

The discovery of Hirst[1] in 1942 that the viruses of influenza A and B would agglutinate chickens' red cells and that influenza antibodies in serum would inhibit this phenomenon has made possible the serologic diagnosis of influenza. A simple and specific laboratory test for influenza has been of particular value not only in the study of epidemics but in the detection of sporadic infections.[4]

In the early spring of 1947 a small epidemic of a mild respiratory illness resembling influenza occurred in this community (Minneapolis). Although this outbreak was not studied locally, mild epidemics of influenza A occurring at the same time have been reported subsequently from California,[5] Michigan,[6] Illinois,[7] Missouri,[8] and New Jersey.[9] The new strains of the influenza A virus causing this outbreak were different antigenically from the PR-8 and Weiss strains, the usual laboratory test strains and the ones used in the preparation of commercial vaccines. Vaccination failed to prevent infection by the strains causing the epidemic. The hemagglutination inhibition test using the PR-8 strain as the test virus failed to show a diagnostic rise in titer in the majority of instances, particularly if the titer of the acute serum was high because of previous vaccination. A high increase in titer was found when a strain of virus isolated in the epidemic was used as the test strain. Occasional patients, however, could be diagnosed using the PR-8 strain. Sigel and his associates[9] demonstrated the diagnostic superiority of the complement fixation test using a soluble antigen prepared from the PR-8 strain which is type specific but not strain specific.

Isolation of a virus from the human myocardium has not been reported. However, the literature supports the concept that a causal relationship exists between acute myocarditis and a preceding infection with influenza and certain other viruses. The advances in the serologic diagnosis of influenza and other virus diseases now permit the collection of clinical data for patients with so-called isolated myocarditis which eventually should give more accurate information as to the etiologic factor.

CONCLUSIONS

1. A case of probable acute myocarditis manifested by congestive heart failure in a young man who recovered is reported.

2. Observations are presented which suggest that the virus of influenza A was etiologically implicated in this instance.

3. Patients with acute isolated myocarditis should be studied clinically more thoroughly than heretofore, making use of the serologic techniques now available in an attempt to establish the etiologic significance of virus infection.

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DUPLICATION OF THE MITRAL VALVE

Case Report and Review of the Literature

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DUPLICATION of the mitral valve is among the rarer of the cardiac anomalies. Of the twelve cases reported in medical literature, all have been found incidentally at autopsy and none have been associated with clinical manifestations attributable to the defect. They offer a problem of interest solely from the viewpoint of developmental malformations of the heart. The example to be presented also was found only incidentally at autopsy.

CASE REPORT

The patient (77205) was a white man who died at the age of 54 years. At 25 years of age he had contracted syphilis. The terminal illness was of fifteen months' duration and was characterized by recurrent congestive failure, precordial pain, and irregular fever. There was hypertension (205/100) and a greatly enlarged heart. The bouts of failure responded only for a transient period to cardiac drugs, diuretics, and antisyphilitic therapy. Terminally, bronchopneumonia developed.

The autopsy (5220) was performed six hours after death. The findings pertinent to the clinical course were anasarca; ascites; hydrothorax; bilateral hypertrophy of the heart (875 grams); severe coronary sclerosis; old myocardial infarction; acute, subacute, and chronic myocarditis; syphilis of aorta and aortic valve with minimal incompetence; arteriolar sclerosis of the kidneys; chronic visceral passive engorgement; and acute bilateral bronchopneumonia.

The mitral valve was formed by two leaflets, the orifice measuring 6 cm. in circumference. The edges and bodies of the leaflets were thin. Long slender chordae extended to a posterior mass of papillary muscles. In the anterior leaflet was an accessory ostium (Fig. 1) lying to the left of the primary opening. It was ovoid in shape, measured 1.0 cm. in its longer diameter, had thin edges, lay 11.0 mm. from the main ostium, and had the appearance of a compressed funnel. There were no distinctly differentiated leaflets. Arising from its free edges were a series of long slender chordae attached to a group of anterior papillary muscles (Fig. 2). Absence of inflammatory reaction was confirmed by microscopic examination.

COMMENT

Greenfield[1] in 1876 reported the first patient with double mitral orifice. The patient was a 28-year-old white man. The smaller accessory orifice, ½ inch in diameter, had two cusps and its chordae were attached to the anterior papillary muscle. The main orifice was normal and the chordae ran to the posterior papillary muscle. Valvular disease was absent. Cohn[2] reported a similar anomaly in a white man of 71 years. The accessory ostium was a slitlike opening but in all other respects the anomaly resembled that of the patient of Greenfield.

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Fig. 1.—View of the opened mitral valve showing the accessory ostium in the anterior mitral cusp.

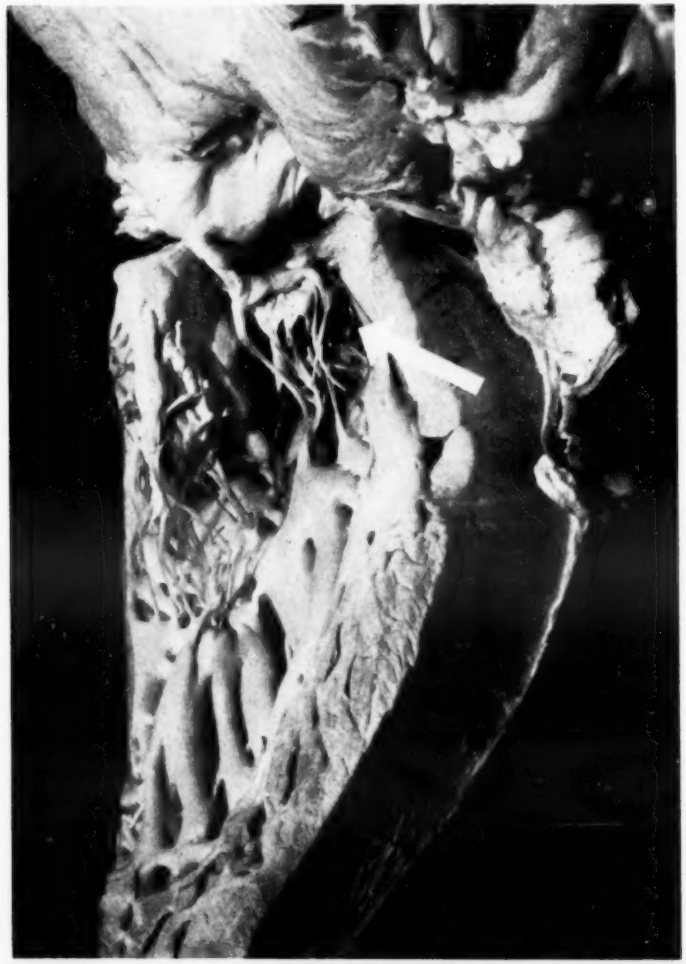

Fig. 2.— View of inferior surface of the accessory ostium (arrow) showing the chordae tendinae attaching to the anterior group of papillary muscles.

In Degen's[3] patient, the two orifices were of equal size, lay in anteroposterior relationship, and had one cusp each, separated by a common connective tissue bridge. Each cusp approximated the bridge on closure, producing a competent valve. Two orifices of equal size were present in a 36-year-old white woman reported by Stuhlweissenburg.[4] The mitral valve was divided into two equal parts by a transverse bridge 25 mm. long by 3.0 mm. wide. The openings were 15 mm. in diameter; one lay anterior and to the left of the other and each had two cusps. The anterior opening showed white nodular thickening; its chordae were short and thick. The posterior opening, its chordae, and the connective tissue bridge were normal. In Camisa's[5] first patient with this anomaly, the smaller orifice measured 45 mm. in diameter and lay anterior to, and to the left of, the larger whose diameter was 5.0 cm. A dense connective tissue bridge, 12 mm. in breadth, joined the mesially placed apex of the anterior opening to the mid-portion of the posterior opening. The bridge was unscarred, and all chordae were long and slender. In the second patient, both ostia were equal in size, 15 mm. in diameter, and were adherent at their apices, forming a connective tissue bridge 11 mm. in breadth. The anterior valve was placed laterally and the posterior medially. The chordae to the anterior and posterior valve were attached to the anterior and posterior papillary muscle groups respectively. In the monograph of Abbott[6], there are two case reports. In the Harvard Museum specimen, a 2-mm. opening in the anterior leaflet of the mitral valve led into an aneurysmal pouch which communicated with the ventricular cavity through numerous fenestrations. The valvular apparatus was not further described. In the specimen from the McGill Museum, the larger orifice lay anteriorly, the smaller posteriorly and 7 mm. from the free edge of the anterior. Each had perfect, well-formed, thin, smooth cusps and slender chordae. The chordae of the anterior opening ran to the anterior papillary muscle, those of the posterior to the posterior papillary muscle. Paul[7] reported an instance of double mitral orifice in a 36-year-old patient, but did not describe it in detail. In Hartmann's[8] patient, the smaller accessory ostium was situated anteriorly, had two poorly defined cusps with small nodular thickenings along the free edges, and was separated from the larger primary opening by a dense connective bridge 8.0 mm. in width. The cusps of the posterior valve had some nodularity of the free edge; each orifice was furnished with slender chordae, those of the accessory ostium attached to a small anterior papillary muscle, those of the posterior ostium to a larger posterior muscle. In a 16-month-old infant, reported by Turpin and Gorin,[9] a rudimentary anterior ostium was present, having one cusp with chordae attaching to the anterior papillary muscle and the region of the anterior and interventricular walls. The posterior orifice was complete; the chordae were attached to a group of posterior muscles. In Davies and Fisher's patient,[10] a white man of 17 years, the accessory ostium was 45 mm. in circumference, lay in the center of the anterior mitral leaflet, was furnished with two cusps well supplied with chordae and papillary muscles, and its line of closure was at right angles to that of the main orifice. The main orifice was 55 mm. in circumference and had a normal structure. As appears evident from these data, the accessory orifice usually lies in the anterior mitral leaflet, has a complete valvular

structure, and is joined with an anterior papillary muscle. Our own example conforms in most respects with these findings, the valve cusps being less distinct than those frequently found.

Associated cardiac anomalies are not infrequent. In Paul's patient[7] there was subaortic stenosis, bicuspid aortic valve, and patent ductus arteriosus. That of Davies and Fisher[10] revealed coarctation of the aorta and a biscupsid aortic valve. In the McGill heart reported by Abbott,[6] persistent ostium primum, bicuspid aortic valve, and a deep auriculoventricular groove were found. A persistent primary ostium was present in the patient of Turpin and Gorin.[9] The double mitral orifice was the sole anomaly found in ours.

Two theories have been advanced to explain the development of a double mitral orifice: (1) that it is of inflammatory origin, (2) that it is the result of developmental malformation. Opinion is about equally divided among observers. Greenfield[1] suggested that adhesions had occurred between the anterior and posterior mitral leaflets during early life and had produced a double orifice. Degen[3] supported this theory in the analysis of his patient. Camisa[5] believed that a fetal endocarditis had been present in his two patients, at which time a smaller amount of blood flowed through the left ventricle, causing the cusps to lie closer together with adhesions more easily occurring. Hartmann[8] felt that in his patient, adherence of the central parts of the original cusps had occurred, the exclusion of the anterior part representing the anlage of the accessory ostium.

The purely developmental basis for the anomaly was supported by Cohn,[2] Stuhlweissenburg,[4] Abbott,[6] Paul,[7] and Turpin and Gorin.[9] Stuhlweissenburg excluded the role of fetal endocarditis in his patient since the bridge and primary ostium were free of endocarditic changes. The pathogenesis suggested by Cohn was that of exaggerated undermining of the endocarditic cushions during the developmental period. According to Abbot,[6] the most tenable theory was that of fenestration of the endocardial cushions in early embryonal life with transformation into a second mitral orifice and adaptive growth of papillary muscle and chordae. Turpin and Gorin[9] found no evidence of inflammatory reaction. Davies and Fisher[10] expressed no opinion as to the developmental or inflammatory background but the presence of other congenital anomalies and the lack of evidence of inflammatory disease are strongly suggestive of developmental origin. The present instance seems the result of a developmental anomaly; there was no evidence of any inflammatory process.

SUMMARY AND CONCLUSIONS

An instance of duplication of the mitral valve is reported and the literature is reviewed. The anomaly apparently may result either as a sequel to fetal endocarditis or from developmental malformation. The current example seems to fall into the second group.

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SUBACUTE BACTERIAL ENDOCARDITIS IN A CHILD, TEN MONTHS OLD, SUCCESSFULLY TREATED WITH STREPTOMYCIN

AXEL AUBERT, AND CHRISTIAN LERCHE

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SINCE the introduction of the newer antibiotics in the treatment of subacute bacterial endocarditis, early diagnosis of this disease has become essential. The causative organism, in the vast majority of the cases, is *Streptococcus viridans*, whose strains most often are sensitive to penicillin.

According to White,[3] the youngest patient with subacute bacterial endocarditis on record is a 1½-year-old child; this case was reported by Goetsch.[2] Because of the age of the subject and because of the successful treatment of subacute bacterial endocarditis due to *Haemophilus influenzae*, the following case is reported.

CASE REPORT

V. E., a girl, 10 months old, was admitted to the Medical Department of the Oslo Municipal Hospital on Feb. 18, 1948. She had been born at term on April 21, 1947. Both pregnancy and delivery had been without complications. The mother had always been healthy. The child was illegitimate and was therefore admitted to an infant home when 1 week old. Her weight was then 3,500 grams.

On Sept. 18, 1947, the consulting physician noted a harsh, loud, systolic murmur over the whole heart and made a diagnosis of congenital heart disease. Otherwise nothing unusual was found and the child gained weight satisfactorily.

On Feb. 4, 1948, she began to cough, and on February 14, her temperature rose to 40.2° centigrade. Fever persisted without any localizing signs except a slight redness and swelling of the left hand for a few days before admission to the Department.

On admission the child did not appear seriously ill. She was a little pale but active and smiling. Her great fontanel was nearly closed. The temperature was 37.9° C., and the pulse was 120 and regular. There was no cyanosis or dyspnea. The tonsils were red and somewhat enlarged. The skin was normal; petechial hemorrhages and enlarged peripheral lymph nodes could not be found. The chest revealed normal expansion and the lungs were clear.

The heart was not enlarged to percussion and the apex beat was not distinctly localized. Over the whole heart a systolic thrill was felt, with its maximum to the left of the sternum in the third and fourth intercostal spaces. On auscultation a loud, harsh murmur was heard, filling the whole systole. It had its maximum point in the third left intercostal space close to the sternal border. The murmur was of Grade 6 intensity (audible with the ear 5.0 cm. from the chest) and was transmitted to the vessels of the neck and was heard over the back of the chest. No diastolic murmur could be detected. The second pulmonic sound was slightly accentuated.

Peripheral vessels appeared normal. There was good pulsation in the femoral arteries. The back of the patient's left hand was slightly swollen and red, and the child cried when the hand was touched even lightly.

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The urine was chemically normal, but on microscopic examination some red and white blood cells were noted. Hemoglobin was 68 per cent, red blood cells numbered 5.2 million and the white cells, 25,200. The blood sedimentation rate was 16 mm. in one hour.

An electrocardiogram showed sinus tachycardia without preponderance of any portions of the heart.

During the days following admission the redness and swelling of the left hand disappeared but the temperature rose and varied betwen 38° and 39° C. with rather high peaks.

An x-ray plate of the heart and lungs showed distinct enlargement of the whole heart, especially on the left side. There was moderate pulsation of the pulmonary arteries although no typical hilus dance could be seen. The lung areas were clear.

A blood culture was taken. Since the diagnosis of bacterial endocarditis was thought to be probable, penicillin therapy was instituted without waiting for the bacteriologic report. The blood culture showed growth of *H. influenzae*, type B. The penicillin treatment was without any effect on the temperature. The strain found in the blood culture was resistant to penicillin since a concentration of 1 International Unit (I.U.) per milliliter of the medium showed growth of the strain, whereas inhibition of growth was obtained with 5 I. U. per milliliter of the medium (the common penicillin-sensitive strain of *Staphylococcus aureus* shows inhibition of growth in a concentration of 0.02 to 0.04 I. U. per milliliter of medium).

On February 26, eight days after admission, the child suddenly became cyanotic and dyspneic; she sat in her bed gasping for air. The extremities were cold and cyanotic and the facial expression anxious. The apex beat was found in the anterior axillary line. Oxygen therapy and lobelin were given immediately; after half an hour the attack was over. Apparently an acute dilatation of the heart had taken place; the exact cause was undetermined.

To check the bacteriologic result a second blood culture was made and again abundant growth of *H. influenzae* appeared.

The patient's serum was examined in a complement fixation test with her own strain as antigen. Strong positive reaction occurred in a serum dose as low as 0.0125.

The strain was now controlled with streptomycin and the result was rather encouraging. The strain showed growth with 7.0 μg. but inhibition of growth with 10 μg. streptomycin per milliliter of medium. Alexander,[5] who has thoroughly studied different strains of a *H. influenzae* type B in patients with meningitis before treatment, found their sensitivity between 1.0 and 13 μg. per milliliter of medium, whereas resistant strains tolerate concentrations of 500 to 1000 μg. per milliliter. With therapeutic doses one may hope to obtain serum concentrations of about 25 μg. per milliliter. (For comparison, it may be mentioned that tubercle bacilli show inhibited growth with 0.50 and *Escherichia coli* with 1 to 4 μg. per milliliter of medium.

Finally, the strain was found to be sensitive to sulfathiazole, as the growth was inhibited in a concentration of 0.10 mg. per milliliter.

Serum against *H. influenzae* type B was not available.

Consequently, on February 27, treatment with streptomycin was instituted. The child's weight was 7.3 kilograms. She received 0.08 Gm. streptomycin intramuscularly every four hours day and night. She was also given 0.25 Gm. sulfathiazole four times a day.

During the first days the disease seemed uninfluenced by the treatment. The temperature remained elevated and the child's weight dropped. Nevertheless, it was encouraging that no growth appeared in blood cultures taken on the second and fourth day of treatment. On the ninth day of treatment the temperature dropped to normal values, and apart from a slight rise the following week it remained normal. Two additional blood cultures were sterile. The weight of the child increased steadily. The drugs were discontinued after nine days of treatment. The patient had received altogether 5.76 Gm. streptomycin and 9.0 Gm. sulfathiazole.

One month after the end of the treatment the child contracted measles, the course of which, however, was uneventful. She was dismissed from the hospital on April 22, in good health. Her weight was 7.8 kilograms. The physical findings over the heart were unchanged. Hemoglobin on dismissal was 78 per cent.

On a follow-up examination on Aug. 19, 1948, the child appeared to have been entirely healthy since her discharge from the hospital. She had had no fever and had shown every satisfactory increase of weight.

COMMENTS

It is hardly possible to tell with absolute certainty whether this child has an open ductus Botalli or a ventricular septal defect. The localization of the maximal systolic murmur may favor the latter diagnosis, whereas propagation of the sound along the vessels of the neck is uncommon in Roger's disease. One may miss the diastolic murmur in persistent ductus Botalli in small children during their first years of life. It lies outside the scope of this paper however, to go into details on this point.

Reports of a few patients with subacute bacterial endocarditis who have been treated and cured with streptomycin have been published. Theoretically, in the present instance, one cannot determine the roles played by sulfathiazole and streptomycin. In bacterial endocarditis due to *S. viridans*, which in vitro is sensitive to both sulfathiazole and penicillin, we know penicillin to be of far greater value than sulfathiazole. We think it reasonable to believe that streptomycin has been the essential drug in the apparent cure of our patient, although we cannot exclude the possibility of some effect of sulfathiazole.

As far as we know, no instance of subacute bacterial endocarditis in so young a patient as ours has heretofore been reported.

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BUNDLE BRANCH BLOCK AS A TEMPORARY PHENOMENON IN THYROTOXICOSIS

Report of a Case

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In so far as we are aware, the following is the first recorded instance of bundle branch block associated with thyrotoxicosis in which normal conduction was restored following partial thyroidectomy. Of added interest is the fact that the patient, a young woman 27 years of age, presented no definite evidence of heart disease following the relief of the thyrotoxicosis. Indeed, all attempts to reinduce the bundle branch block after thyroidectomy were unsuccessful.

A review of the literature concerning the association of bundle branch block with hyperthyroidism discloses only fifteen instances in all. Five were reported by Gordon, Soley, and Chamberlain;[1] four of their patients were over 42 years of age, the fifth was 31 years old, and in all the conduction defect was ascribed to coexisting coronary heart disease. Five more instances of right bundle branch block were mentioned by Goodall and Rogers,[2] who did not describe the age or the sex of the patients. Coelho[3] described one instance of prolonged QRS duration without giving any clinical details. Dameshek[4] described one instance in a 60-year-old woman. Ramos, DeMelo, and Ferraz[5] found two patients with bundle branch block among seventy hyperthyroid patients. Rose, Wood, and Margolies[6] presented the report of a 29-year-old woman whose right bundle branch block had persisted for the three years of observation, and who had shown no other evidence of heart disease. The rarity of bundle branch block in thyrotoxicosis is further emphasized by the fact that no mention of bundle branch block is made in several comprehensive articles on the electrocardiogram in hyperthyroidism[7-14] and in the standard texts, only Thomas[15] mentions the occurrence of bundle branch block in thyrotoxic heart disease. In no case report that we have seen has there been described reversion to normal intraventricular conduction after treatment of the hyperthyroidism.

CASE REPORT

F. K., a 27-year-old unmarried woman, serving in the Women's Reserve of the United States Navy, was referred to the cardiac clinic on May 30, 1944, for examination. Past history

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Opinions or conclusions contained in this report are those of the authors. They are not to be construed as necessarily reflecting the views or the endorsement of the Navy Department.

revealed that she was born and had spent most of her life in the Middle West and had had the usual childhood diseases. At the age of 11 years she developed a simple goiter; she was treated with iodized salt and remained asymptomatic. There was no history of rheumatic fever, scarlet fever, diphtheria, heart disease, or kidney disease. An appendectomy had been performed in January, 1944. The present illness began insidiously during the spring of 1944. The patient's only complaint was of rapid heart action, although later on she recalled a 5-pound weight loss, slight nervousness, irritability, and a fine tremor of the hands.

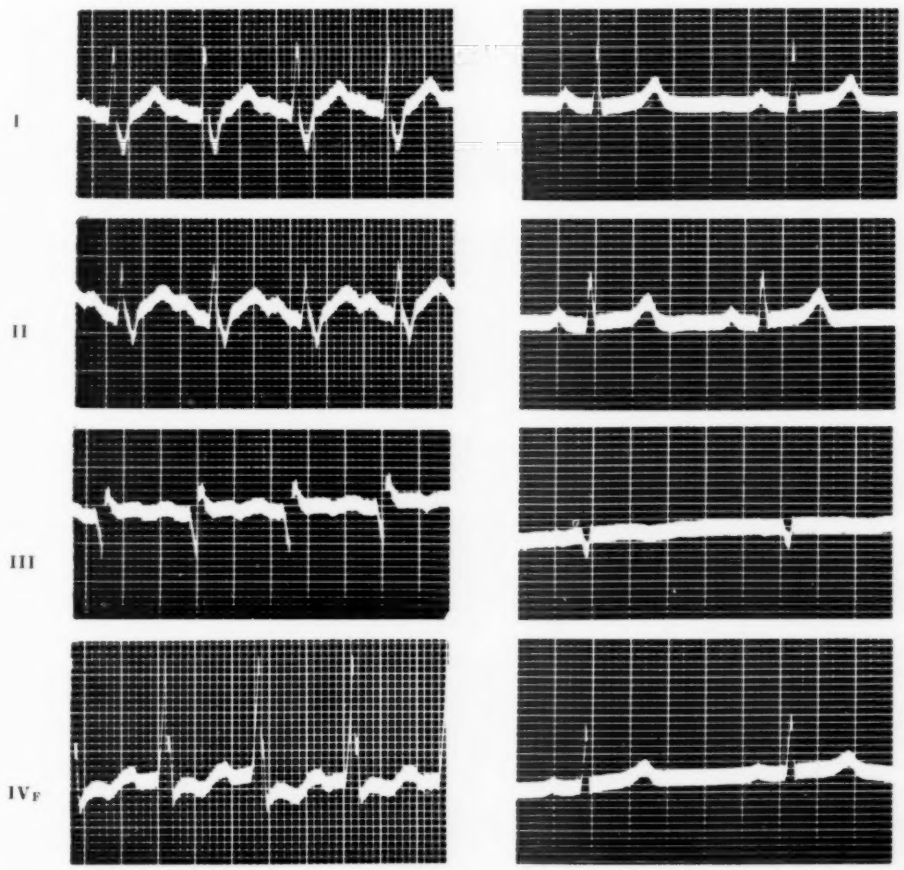

Fig. 1.—*A*, bundle branch block during thyrotoxicosis. *B*, normal rhythm following thyroidectomy.

Physical examination revealed a slightly overweight, nervous woman with exophthalmos. The thyroid gland was large and firm without nodules, the right lobe being larger than the left; both a bruit and a thrill were present. The skin was warm, and there was a continuous fine tremor of the hands. The heart was not enlarged, the blood pressure was 160/82, the rhythm was regular at 132, and a faint pulmonary systolic murmur was heard which became louder when the patient was recumbent. The remainder of the physical examination disclosed no abnormalities.

X-ray examination of the heart was reported as follows: "Lungs clear. Aortic configuration of the heart and slight elongation of the aorta." The basal metabolic rate was +35 and +40 per cent. An electrocardiogram (Fig. 1,*A*) showed a heart rate of 120 and right bundle branch block with the QRS duration 0.13 second. Blood cholesterol was 125 mg. per 100 c.c. of blood.

The patient was transferred to the hospital. After preparation with Lugol's solution, she underwent a partial thyroidectomy on July 3, 1944. A bilaterally enlarged diffuse toxic goiter was found at operation. Her symptoms disappeared and she was discharged to duty on August 12, 1944.

Except for one week's hospitalization for sinusitis in September, 1944, the patient was well until Dec. 20, 1945, when she contracted scarlet fever. Her convalescence was slow and was

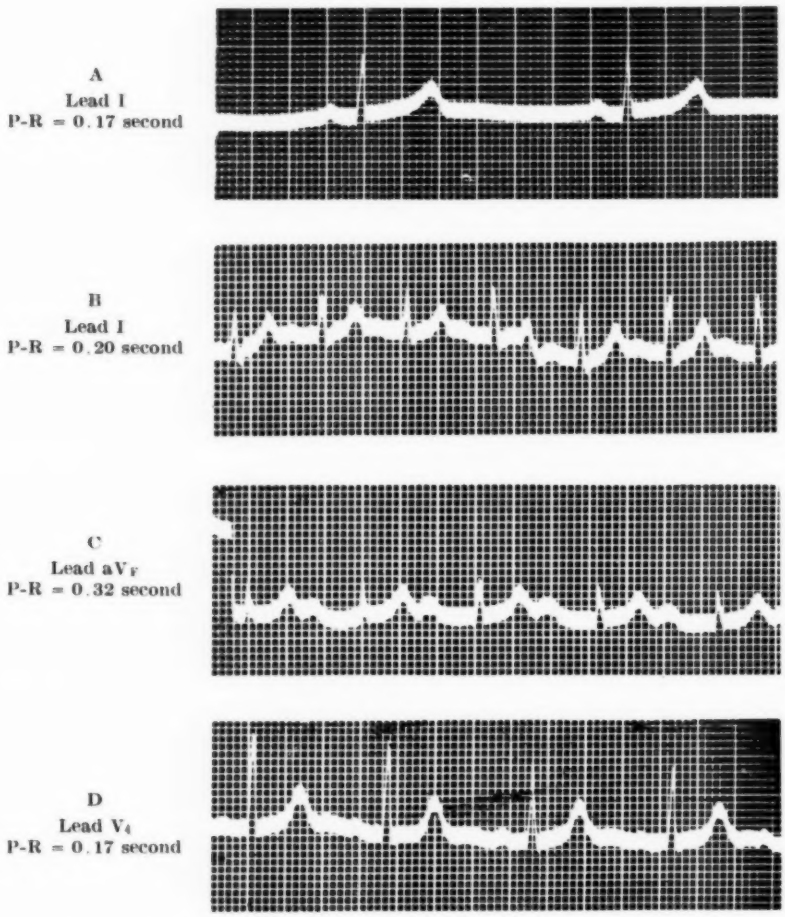

Fig. 2.—Changes in the P-R interval before exercise (*A*), and after exercise (*B*, *C*, and *D*.)

complicated by a recurrence of hyperthyroidism. The basal metabolic rate on several occasions was +45 per cent. One electrocardiogram was taken and reported as showing a QRS duration of 0.12 second with slurred QRS complexes, but the tracing was not preserved. In February, 1946, the patient underwent a second sub-total thyroidectomy. The report of the pathologist was "toxic hyperplasia of the thyroid showing regressive change." Following operation the basal metabolic rate was +4 per cent. In June, 1946, the patient was again seen in the cardiac clinic. The electrocardiogram taken at that time (Fig. 1,*B*) showed normal conduction at a rate of 62.

During the following year the patient gradually developed symptoms of hypothyroidism, with basal metabolic rates ranging from −20 to −30 per cent. Treatment with thyroid extract, 1½ grains daily, raised the basal metabolic rate to about −15 per cent and caused the symptoms to disappear.

In October, 1947, an attempt was made to see if the bundle branch block would recur following exhausting exercise on the treadmill. Intraventricular conduction remained normal, but partial A-V block did develop transiently as shown by an increase in the duration of the P-R interval from 0.17 to 0.32 second at a maximum heart rate of 140 per minute (Fig. 2).

A second attempt was then made by giving the patient 6 grains of thyroid extract daily for two weeks. Twice weekly her basal metabolic rate was determined and electrocardiograms were taken before and after exercise. During this time the basal metabolic rate rose from −20 to −3 per cent and the resting pulse from 45 to 60 beats per minute. The electrocardiograms again showed transient lengthening of the P-R interval after exercise but at no time did any change appear in the QRS complexes.

In view of the reported occurrence [16] of bundle branch block following fright, a third attempt to reinduce the block was made by firing a rifle unexpectedly under the bed on which the patient was lying while having an electrocardiogram recorded. No conduction abnormalities developed, although the tracing showed lowering of the T waves in Lead II.

Four years after the first discovery of bundle branch block, the patient had no cardiac symptoms, and the physical examination revealed no abnormality. The pulmonary systolic murmur had disappeared and the blood pressure was 110/72. The report of an x-ray examination of the heart was as follows: "Re-examination of the chest reveals slight decrease in the cardiac measurements and in the cardiothoracic ratio since the previous examination in 1944." The electrocardiogram was within normal limits with the subject at rest.

DISCUSSION

We have ascribed the bundle branch block in this patient to hyperthyroidism, for it was present in so far as we know only when the patient had an elevated metabolic rate, and it was not reproduced during the tachycardia caused by exercise or by being startled. There was no evidence of pre-existing heart disease, nor was there any evidence of organic heart disease four years after operation. The fact that bundle branch block is rare in young women makes the chance finding of a transient bundle branch block in our patient a most remote possibility. Whether or not a relationship exists between the lengthening of the P-R interval following exercise noted in the last examinations, and the occurrence of the bundle branch block during thyrotoxicosis is not known.

The mechanisms by which hyperthyroidism causes cardiac abnormalities have been the subject of much discussion. Most authors are agreed that the development of hyperthyroidism in an individual with pre-existing organic heart disease will cause earlier onset of failure due to the increased demands made upon the circulatory system by the hypermetabolism. Several theories have been put forward, however, in an attempt to explain how thyrotoxicosis can cause reversible arrhythmias and congestive failure in the apparently normal heart. An early, and now largely discarded, explanation of the problem ascribed the cardiac strain to pressure of the enlarged thyroid upon the trachea, veins, or cardiac nerves. Later a toxin liberated by the thyroid was hypothesized, with specific action localized in the myocardium. Goodall and Rogers[2] supported this theory with post-mortem evidence of focal myocardial necrosis in nine patients with thyrotoxicosis. At present, as summarized by Rose,[17] the cardiac abnormalities seen in

thyrotoxicosis are generally ascribed to: (1) increased cardiac work secondary to increased body metabolism, (2) increased metabolism of the heart muscle itself, and (3) the influence of pre-existing or coincidental cardiovascular disease. In the case reported, there is insufficient evidence to add weight to any theory, although it is tempting to postulate a focal lesion, such as Goodall and Rogers describe, interfering with conduction through the right bundle branch.

SUMMARY

1. A report of hyperthyroidism and associated right bundle branch block in a young woman is presented, and the literature concerning the coexistence of these two conditions is reviewed.

2. It is believed that this is the first reported instance in which intraventricular conduction returned to normal after treatment of the hyperthyroidism.

3. Right bundle branch block is added to the other well-known functional abnormalities of the heart in hyperthyroidism which may disappear after thyroidectomy.

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Abstracts

Selected Abstracts

Tarail, R.: Relation of Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances. Am. J. Med. 5:828, (Dec.) 1948.

The author attempts to determine the relationship between abnormalities in the concentration of serum potassium and electrocardiographic findings. The study is based on a survey of the concentrations of serum potassium and of concomitant electrocardiograms in nineteen patients with severe renal insufficiency and in five patients with diminished and, subsequently, normal concentrations of serum potassium. Four of the patients with renal insufficiency had electrocardiographic findings referable to the toxic effect of potassium when the concentration of serum potassium was elevated.

Electrocardiographic disturbances sometimes occurred when the range of concentration of serum potassium was 6.8 to 7.6 mEq. per liter. These disturbances were present consistently at concentrations greater than 7.8 mEq. per liter. At a given elevated concentration, the appearance of the electrocardiogram varied widely.

Peaked T waves and increase in the duration of the QRS complex were the most characteristic changes associated with hyperkaliemia while low amplitude of the T wave and prolonged electrical systole were the most frequent findings in the group with hypokaliemia.

The electrocardiogram is believed not to be a proper substitute for the measurement of the concentration of serum potassium.

WOODS.

Nadler, C. S., Bellet, S., and Lanning, M.: Influence of the Serum Potassium and Other Electrolytes on the Electrocardiogram in Diabetic Acidosis. Am. J. Med. 5:838 (Dec.), 1948.

The authors have studied the relationship between changes in the serum potassium and other electrolytes and the electrocardiogram in forty-five patients with diabetic acidosis.

Before therapy was begun it was found that the serum potassium concentration in this group of patients varied from a normal to a greatly elevated level. In those patients with elevated serum potassium concentration, electrocardiographic tracings showed an increase in T-wave amplitude with a narrow base without prolongation of the Q-T interval.

Soon after insulin therapy was begun the serum potassium levels usually dropped rapidly to a concentration below normal. At this time the electrocardiograms showed a prolongation of the Q-T interval and low or inverted T waves. The changes in the Q-T interval were most characteristic in the precordial leads. Of these, CR_3 proved to be the most informative lead. The relationship between the prolongation of the Q-T interval above normal and the serum potassium level showed a high degree of correlation. In this group of patients there was no significant degree of correlation between the percentage of increased duration of the Q-T interval above normal and the serum calcium level or the carbon dioxide tension. Administration of potassium chloride at a time when the electrocardiogram showed changes suggestive of a low serum potassium resulted in the return of the Q-T interval to a normal duration.

Although a significant correlation was found between the height of the T wave and blood pH and carbon dioxide tension, correlation between the height of the T wave and the serum potassium

concentration was significant only when the plasma concentrations were elevated. However, observations on the effect of intravenous potassium chloride showed a definite qualitative relationship. When the serum potassium was high, the T wave was tall with a narrow base, whereas the T wave was diminished in amplitude or inverted when the serum potassium level was below normal.

In a small number of patients with diabetic acidosis, a U wave was found in the electrocardiogram when the serum potassium concentration was below normal. It disappeared during intravenous administration of potassium chloride. The occurrence of depressed RS-T segments was apparently related to the degree of cardiovascular shock present in many of the patients, although there may be some relationship with the serum potassium level.

The authors believe that the electrocardiogram offers a valuable means of following, in a crude way, the serum potassium level during the treatment of patients with diabetic acidosis.

SCHWARTZ.

Leimdorfer, A.: The Electrocardiographic Response to Changes of Posture During Respiratory Arrest Following Deep Inspiration or Expiration. Ann. Int. Med. **29**:1043 (Dec.), 1948.

Electrocardiograms were obtained on sixty-five healthy persons of both asthenic and pyknic builds and on 116 cardiac patients without congestive heart failure. Among the cardiac patients were twenty with valvular disease, thirty-two with coronary artery disease, forty-five with myocardial disease, ten with essential hypertension, five with nephritis and hypertension, and four with hyperthyroidism.

Electrocardiograms were taken in the recumbent position (a) during normal respiration, (b) in respiratory arrest after maximal inspiration (Period I), and (c) in respiratory arrest after maximal expiration preceded by maximal inspiration (Period E). The subjects were then requested to stand for fifteen minutes. At the end of this period while the subject remained standing, electrocardiograms were again obtained in the same manner. The subjects then resumed the recumbent position and clinostatic electrocardiograms were obtained at intervals during normal respiration. Three standard leads and usually two chest leads were used at the fourth intercostal space at the left border of the sternum (CR_2) and a little outside the apex in the fifth intercostal space (CR_4) with the right arm as the site of the indifferent electrode. Slipping of the electrode was prevented by bandages.

In healthy persons of both asthenic and pyknic builds, alterations in the electrocardiogram, especially in the final deflection, took place during Period I in the standing position but disappeared in Period E. In contrast, many cardiac patients showed pathologic electrocardiographic changes in Period I and further in Period E in the upright position. In one group of patients, who did not show any pathologic electrocardiogram in the recumbent position, pathologic changes appeared in the final deflection in Period I in the standing position and did not disappear in Period E. Similarly, pathologic electrocardiographic changes in persons with myocardial defects or coronary disease were aggravated in Period E during standing position. Such alterations (depressions of RS-T segments and isoelectric or inverted T waves) were observed in Lead I or Lead II and in the chest leads.

The author suggests that these supplementary procedures may be of some prognostic value in that alterations noted during the upright position should disappear quickly on resumption of the recumbent position when the myocardial disease is mild, whereas, if the myocardial disease is severe, the return of the electrocardiogram to its original pattern will be delayed when the subject resumes the recumbent position. He has also observed that the changes in the orthostatic record which he interprets to be indicative of myocardial disease can be obtained in patients with neurocirculatory asthenia. The differentiation in such cases must then be made on the basis of collateral clinical findings. He did not subject his patients with a "positive result" to the anoxemia or exercise test, but he states that his technique has an advantage over these other procedures because he has not encountered any untoward reactions.

WENDKOS.

Wolf, S., Pfeiffer, J. B., Ripley, H. S., Winter, O. S., and Wolff, H. G.: Hypertension as a Reaction Pattern to Stress; Summary of Data on Variations in Blood Pressure and Renal Blood Flow. Ann. Int. Med. **29**:1056 (Dec.), 1948.

Renal vasoconstriction and arterial hypertension constitute an atavistic protective reaction to sudden stress. This particular reaction, when frequently repeated in fundamentally aggressive individuals who are faced with day-to-day stresses and threats arising out of problems of interpersonal relations, eventually becomes a permanent and irreversible disturbance in some cases. In others, it may be sustained until the tensions which are responsible are removed by appropriate psychotherapy. Dye excretion studies which measure renal blood flow and glomerular filtration indicate that both the afferent and efferent glomerular arterioles participate in the renal vasoconstriction which accompanies the hypertensive state in man. It is also possible to demonstrate by similar techniques that even though the hypertensive subject who has been subjected to thoracolumbar sympathectomy, will continue to manifest an elevated blood pressure in response to situational threats, the rise in the blood pressure following the operation is accompanied by constriction of only the afferent arterioles of the kidney.

WENDKOS.

Middleton, W. S.: Infectious Arteritis. Ann. Int. Med. **29**:1093 (Dec.), 1948.

In general, infectious arteritis results from direct invasion of the vessel by the etiological agent or from sensitization to bacterial or nonbacterial allergens. In the former group can be included the vascular lesions which accompany the rickettsial diseases or the visceral spread of a syphilitic infection. In the latter group can be included periarteritis nodosa, thromboangiitis obliterans, and the vascular lesions of rheumatic fever. Infectious arteritis forms the dominant feature of the rickettsial diseases, periarteritis nodosa, and thromboangiitis obliterans. In all of these diseases, the entire picture is directly related to the vascular inflammation. The acute inflammatory phase of the infectious arteritis determines the clinical expression of the rickettsial diseases and its subsidence marks the period of recovery in their course. Periarteritis nodosa and thromboangiitis obliterans are characterized by just as specific vascular changes but significantly in these diseases the processes of repair determine even more serious nutritional changes in the involved part than does the acute infectious phase. Rheumatic fever and syphilis represent a somewhat different situation. The effects of rheumatic and syphilitic arteritis are dependent upon long, continued subnutrition with degeneration and fibrosis rather than upon the pathologic changes of the acute vascular damage.

WENDKOS.

Shelburne, P. A.: Primary Sarcoma of the Heart. Ann. Int. Med. **29**:1139 (Dec.), 1948.

Repeated reaccumulations of pericardial effusion, a febrile course, bouts of Adams-Stokes seizures, cardiac arrythmias, and terminal cardiac failure were the chief features which characterized the illness of a 29-year-old white man, which terminated fatally. During life, the presence of a malignant lesion of the heart was not suspected. At autopsy, the following pathologic changes of the heart were noted. The pericardial cavity was completely obliterated by old fibrous adhesions. The heart with its pericardial covering weighed 1,500 grams. Almost the entire myocardium had been replaced by tumor tissue and the wall measured up to 10 cm. in thickness. There was a large tumor mass, rather necrotic, growing from the wall into the right ventricle, practically filling this chamber, and, pointing upward, partially occluding the orifice of the pulmonary artery. The left side of the heart showed extensive involvement of the auricular wall, which averaged 3.5 mm. in thickness. There were also isolated areas of tumor tissue in the myocardium of the left ventricle. The valves all appeared competent and showed no evidence of disease. Microscopic study of the heart sections revealed that they were neoplastic growths made up of ovoid and spindle-shaped cells. Extensive necrosis affected a greater part of the tumor tissue. The myocardium showed definite invasion by the neoplastic process.

WENDKOS.

McCandless, F. D., and Faloon, W. W.: The Diagnosis of Metastatic Tumor by Cytological Examination of the Pericardial Fluid; Report of a Case Using Shorr's Stain. Ann. Int. Med. **29**:1157 (Dec.), 1948.

The authors describe a case of bronchogenic carcinoma with metastases to the pericardium in which the diagnosis was established during the life of the patient by the identification of neoplastic cells in aspirated pericardial fluid as well as in sputum. Shorr's staining method was used and the details of this procedure are given. The advantages and possibilities of this diagnostic technique are discussed especially so far as they relate to the diagnosis of metastatic lesions involving the heart.

WENDKOS.

Pearl, F.: Tetraethyl Ammonium Chloride—Its Effects on Surface Temperatures of Extremities in Peripheral Vascular Conditions. Ann. Surg. **128**:1092 (Dec.), 1948.

The vasodilator effect of tetraethyl ammonium chloride was studied in a series of patients, eight of whom were suffering from peripheral vascular disorders. By means of a skin temperature thermocouple, the changes in cutaneous temperature of the digits were studied.

From the results, it was concluded that the alterations were variable, undependable, and of short duration, and that tetraethyl ammonium was unsuitable as a diagnostic method in estimating the degree of vasoconstrictor tone in the extremities. Furthermore, the experiments were interpreted as casting doubt on the efficiency of the drug as a vasodilating agent in peripheral vascular disease.

ABRAMSON.

Taquini, A. C., Fasciolo, J. C., Suarez, J. R. E., and Chiodi, H.: Respiration and Circulation in Pulmonary Anoxemia. Arch. Int. Med. **82**:534 (Dec.), 1948.

To estimate the importance of carbon dioxide and/or hydrogen ion in circulatory and respiratory adjustment, data in patients with Ayerza's disease were compared with those secured in patients with anoxic conditions without carbon dioxide retention, that is, in patients at high altitude and in those with congenital heart disease. This paper deals with pulmonary anoxia (anoxic anoxia due to impairment of the pulmonary function, with low arterial oxygen tension and carbon dioxide retention).

Determinations were made on eighteen patients with different degrees of pulmonary fibrosis and emphysema. Pulmonary ventilation was found slightly increased; alveolar carbon dioxide tension was found to be higher and oxygen tension lower than in normal persons, indicating that alveolar ventilation was impaired. This alveolar hypoventilation in patients in whom pulmonary ventilation was normal or even increased is produced by poor efficiency of ventilation because of uneven distribution of gases in the lung and diminution of tidal air.

The main pulmonary disturbance of the group with Ayerza's disease was emphysema of the lung, as reflected by the figures of the total pulmonary capacity and its subdivisions. Vital capacity was found to be diminished, mainly because of a reduction of complemental air, reserve air being about normal. Residual air was increased, and total pulmonary capacity was slightly reduced. The oxygen capacity of blood was increased, keeping an inverse coarse correlation with the arterial oxygen pressure. Arterial oxygen saturation and pressure were reduced below normal values in all the patients. The oxygen content of arterial blood of the group with Ayerza's disease was slightly elevated when compared with that in normal persons at sea level. That the arterial anoxemia was stimulating the breathing in the patients, probably through the carotid and aortic bodies, was shown by the depression of ventilation produced while they were breathing pure oxygen, during which time the arterial carbon dioxide pressure increased with a decrease in the pH. The response to inhalation of carbon dioxide was less than that of normal persons. Circulation times were prolonged in almost every case and blood volume was increased (primarily because of an increase in red cell volume). Cardiac output was maintained at normal levels in cases uncomplicated by cardiac failure.

BERNSTEIN.

Rather, L. J.: Acquired Acute Hemolytic Anemia of Unknown Cause. Arch. Int. Med. **82:**578 (Dec.), 1948.

A fatal case of acquired acute hemolytic anemia of unknown etiology occurring in a 20-year-old white woman is presented and the clinical course, available laboratory data, and autopsy findings are reviewed. No abnormality of the erythrocyte was demonstrated, but it is clear from the data that transfused red cells were destroyed as fast as they were given.

The lesions at necropsy consisted of disseminated fibrinoid arteritis, atypical pneumonia, and lower nephron nephrosis. The arterial lesions were indistinguishable from those seen in lupus dicceminatus or periarteritis nodosa, and the atypical pneumonia resembled the type described as characteristic of pneumonitis seen in rheumatic fever and in sensitization to sulfonamide drugs. It seems possible that the hemolysis, the vascular lesions, and the pneumonitis were all expressions of damage caused by a circulating antigen to which the patient was sensitized.

BERNSTEIN.

Siems, L. L., Kosman, A. J., and Osborne, S. L.: A Comparative Study of Short Wave and Microwave Diathermy on Blood Flow. Arch. Phys. Med. **29:**759 (Dec.), 1948.

Using pentobarbital-anesthetized dogs, the authors investigated the effect of short wave and microwave diathermy on the flow of blood through the femoral artery, utilizing bubble flow meters. Varying degrees of nervous denervation of one extremity were produced twelve weeks before the study was performed. In one group, complete motor paralysis was obtained; in a second, there was a combined motor and sensory loss; while in the third, there was motor, sensory, and autonomic loss.

It was found that short wave and microwave diathermy are equally effective in eliciting an increased blood flow in the hind limbs of normal dogs. In the sympathetic denervated limb these procedures produced no augmentation in circulation. From such evidence it was concluded that the integrity of the sympathetic outflow in the dog is necessary for the typical vascular response to local heating.

ABRAMSON.

Groen, J., and Godfried, E. G.: The Occurrence of Normoblasts in the Peripheral Blood in Congestive Heart Failure: An Indication of Unfavorable Prognosis. Blood **3:**1445 (Dec.), 1948.

Nine patients with severe congestive heart failure, all showing a varying number of normoblasts in the peripheral blood, are reported. A similar number reported in the literature are cited. In some, there was a remission during which the normoblasts disappeared, but all of these patients died. Eight of the authors' patients lived thirteen days or less from the time the normoblasts were first noted.

Autopsies revealed thrombi within the heart, pulmonary infarcts, or both. It was felt that these lesions in addition to the congestive heart failure, resulted in marked interference with oxygenation of the blood, and in this way caused the normoblastosis.

A search for normoblasts in the blood of patients with severe heart failure is recommended, since this seems to indicate that the condition is complicated by thrombi or emboli in the lesser circulation and is thus a sign of a poor prognosis.

BEIZER.

Massell, B. F., Dow, J. W., and Jones, T. D.: Orally Administered Penicillin in Patients With Rheumatic Fever. J. A. M. A. **138:**1030 (Dec. 4), 1948.

A group of thirty-seven children with rheumatic fever who harbored hemolytic streptococci in their throats were treated with divided oral doses of penicillin totalling from 300,000 to 1,000,000 units per day for a period of ten days. Suppression of the growth of the organism during the course of therapy occurred in all but four patients and complete eradication following cessation of treatment was demonstrated in all but eight instances. Of ten clinical and five subclinical hemolytic streptococcal infections in patients with rheumatic fever who were promptly treated with peni-

cillin, there were no recurrences of rheumatic fever. The mass administration of penicillin orally in doses of 100,000 units three times daily seemed to halt abruptly an outbreak of hemolytic streptococcal infection among ward patients. The barring of visitors and the discontinuing of new admissions during this period, however, may also have played a role in preventing the development of new cases of infection.

It is suggested that oral rations of 100,000 to 200,000 units of penicillin administered three times a day, by preventing further hemolytic streptococcal infections, may prove to be of value in rheumatic fever prophylaxis in susceptible youngsters. The danger of producing penicillin-resistant strains of hemolytic and nonhemolytic streptococci involved in such a program remains to be more fully evaluated.

HANNO.

Friedell, M. T.; Drucker, E. F.; and Pickett, W. J.: Histidine and Ascorbic Acid Treatment of Arteriosclerosis Obliterans. J. A. M. A. **138:**1036 (Dec. 4), 1948.

A group of twenty-five patients who were hospitalized for proposed amputation because of gangrenous changes of the lower limbs or evidences of impending gangrene as the result of obliterative arteriosclerotic disease of the lower extremities were treated with l-histidine monochloride and ascorbic acid for a minimum of ten days. All of the patients had previously failed to respond to bed rest, the use of vasodilator drugs, and sympathetic block. None of the patients showed pulsations below the popliteal fossa, and in only five of the patients were popliteal pulsations noted.

Thirteen of these patients (twelve men and one woman), ranging in age from sixty-four to eighty-one years, received oral doses of 2.0 Gm. of histidine and 400 mg. of ascorbic acid three times daily. Less than one-half of the group experienced good relief from rest pain. The two ambulatory patients with intermittent claudication were both able to walk better, and in one patient with a palpable popliteal pulsation there was a return of the posterior tibial and dorsalis pedis pulsations. Of eight patients with gangrene, rapid demarcation occurred in three and continued extension in five.

Twelve of the patients (nine men and three women), ranging in age from 50 to 81 years, were treated parenterally with 5 c.c. of a 4 per cent solution of histidine and 100 mg. of sodium ascorbate every six hours; in addition, these patients were also given 600 mg. of ascorbic acid per day, orally. Relief from pain occurred in a majority of patients treated parenterally. Good demarcation occurred in two of the six patients with frank gangrene. Circulation studies with radioactive phosphorous in eleven of the patients receiving parenteral histidine therapy showed indications of some improvement in the circulation of the involved limb in eight of the patients.

Of the twenty-five patients treated by either the oral or parenteral routes, six were discharged as improved, eleven came to amputation, six were unimproved, and two died. No evidences of toxicity from histidine were noted.

HANNO.

Fershtand, J. B., and Beavers, G. H.: Complete Heart Block in Pregnancy. J. A. M. A. **138:**1040 (Dec. 4), 1948.

A 34-year-old pregnant white woman was known to have had heart disease since the age of 12 years. There was no history of rheumatic fever. An electrocardiogram taken in the third month of her pregnancy revealed a first degree A-V heart block (P-R interval, 0.22 second) and intraventricular conduction defect (QRS interval, 0.12 second). A double mitral murmur was found on auscultation. Because of some degree of progressive cardiac enlargement during the succeeding four months, the patient was digitalized. Without instruction the patient increased her daily digitalis dosage from 1½ to 4½ grains, and several days later complained of fatigue and palpitation. Electrocardiographic study showed a complete A-V heart block with widened ventricular complexes identical with those demonstrated in her earlier tracing. Digitalis was discontinued and the patient was put at bed rest for the remainder of her pregnancy. An electrocardiogram taken in the ninth month showed persistence of the complete A-V block and the presence of occasional ectopic ventricular beats. Delivery by section was decided upon, and a continuous tracing taken during the operation showed a 2:1 A-V block with prolongation of the A-V and intraventricular conduction times. The patient was delivered of a normal child.

The patient was discharged three weeks following section, and serial electrocardiographic tracings taken periodically during the first seven months post partum all revealed complete A-V heart block.

The authors believe that this woman had rheumatic mitral disease and a congenital interventricular septal defect. They postulate that the ischemia secondary to the heart strain resulting from the pregnancy added to the pre-existing damage to the bundle of His, and that variations in the degree of relative anoxemia of the bundle probably produced the variations in the degree of A-V block.

HANNO.

Boyer, N. H., and Weinstein, L.: Diphtheritic Myocarditis. New England J. Med. **239:**913 (Dec. 9), 1948.

The authors studied ninety-three unselected diphtheria patients with frequent serial electrocardiograms. The ages of the patients ranged from 3 to 72 years, but 64.3 per cent were below 20 years of age. The degree of electrocardiographic abnormality was graded from 1 to 4. Sixty-one patients (65 5 per cent) showed incontestable abnormalities; of these, the majority (65.5 per cent) were slight and usually transient. Multiple deviations from the normal were more usual than isolated ones, although variations in the RS-T segment or T waves, or both, not infrequently occurred alone. It is noteworthy that one patient with ventricular tachycardia for a short period had only minor electrocardiographic findings before and after the period of rapid pulse. This was the only one of the group of patients with myocarditis of the most severe degree who survived. Age did not seem to determine the degree of electrocardiographic aberration. The average time of onset of electrocardiographic abnormalities was eleven and one-half days after the inception of the diphtheria. The development and evolution of electrocardiographic abnormalities did not appear to be related to the type of organism.

The over-all mortality (Table 6) was 14.4 per cent for the series. There were no deaths among the patients who had normal or borderline electrocardiograms. The number of deaths rose steadily with increase in intensity of the electrocardiographic aberrations, being 5 per cent in the patients with Grade 1, 14 per cent in those with Grade 2, 40 per cent in those with Grade 3 and 78 per cent in those with Grade 4 changes. The high incidence of electrocardiographic abnormalities in this series is attributed by the authors to the fact that frequent or daily records were made during the early and later phases of the illness. Frequent electrocardiograms appeared to provide the only certain means of detecting myocarditis, since reliable physical signs of heart disease were never present in patients with the lesser grades of deviation from the normal and those with a high degree of electrocardiographic abnormality often revealed surprisingly little on physical examination of the cardiovascular system.

The demonstration of marked changes in the heart muscle at necropsy makes it difficult to escape the conclusion that patients who do not die but who have electrocardiographic abnormalities of relatively the same degree as some of those who expire have lost a fair portion of the myocardium. Reversability of the electrocardiographic changes cannot be considered as indicating a return to normal of the myocardium. In a patient who died of bronchopneumonia on the forty-seventh day of diphtheria, the electrocardiogram taken just before death showed reversion toward normal, and yet at autopsy there was a severe degree of myocardial fibrosis. Although the evidence indicates that recovery is complete enough in the young patient, it seems illogical to assume that such hearts have a normal reserve for later life, should hypertension or coronary artery disease make its appearance.

WENDKOS.

Lagerloef, H., and Werkoe, L.: Studies on the Circulation in Man. Acta cardiol., **4:**1, 1949.

The action of an intravenous dose of 0.8 mg. lanatoside C was studied in five patients with congestive heart failure and in seven patients with heart disease but not in failure. Cardiac output, and pressures in the right auricle, right ventricle, and pulmonary and brachial arteries were determined by means of right heart catheterization before, and at various intervals after the administration of digitalis.

Cardiac output invariably rose in the patients with heart failure while the response in the others sometimes consisted of an increase, sometimes of a decrease in output. The pressures in general remained unchanged, though sometimes the right auricular pressure decreased and the arterial pressure increased. There was no apparent correlation between auricular pressure and cardiac output.

The significance of these findings is discussed, especially with regard to McMichael's theory of digitalis action which is not confirmed by this study.

LUISADA.

Selzer, A., Carnes, W. H., Noble, Jr., C. A., Higgins, Jr., W. H., and Holmes, R. O.: The Syndrome of Pulmonary Stenosis With Patent Foramen Ovale. Am. J. Med. 6:3 (Jan.), 1949.

The authors report two adult cases of pulmonary stenosis with intact interventricular septum and patency of the foramen ovale. In addition they analyze twenty-seven autopsy reports gathered from the literature. The findings in all the available autopsy reports are summarized and contrasted with the clinical and pathologic features of proved cases of the tetralogy of Fallot and the Eisenmenger complex.

Chronic cyanosis, polycythemia, and clubbing were present in all these patients. However, patients with pulmonary stenosis with both auricular and ventricular septa closed are usually noncyanotic. In pulmonary stenosis a systolic murmur is heard in the majority of patients in the pulmonic area whereas in the tetralogy of Fallot and the Eisenmenger complex it is more often heard along the lower left sternal border. Electrocardiographic examination is not of particular value in differential diagnosis since all the lesions under discussion are usually associated with right axis deviation.

Particularly helpful from the standpoint of the differential diagnosis of pulmonary stenosis with intact interventricular septum and patency of the foramen ovale is the x-ray finding of a post-stenotic dilatation of the pulmonary artery which shows diminished or absent pulsations and lung fields which are more radiolucent than normal. This is in contrast with the small shadows of the pulmonary vessels in the tetralogy of Fallot and the dilated and congested pulmonary vessels of the Eisenmenger complex.

Pulmonary stenosis with patent foramen ovale is a clinical entity with enough distinctive features to make diagnosis possible during life and represents an exception to the rule that cyanotic congenital heart disease with dilated pulmonary arteries is usually unsuitable for surgery.

SCHWARTZ.

Greene, D. G., Baldwin, E. deF., Baldwin, J. S., Himmelstein, A., Roh, C. E., and Cournand, A.: Pure Congenital Pulmonary Stenosis and Idiopathic Congenital Dilatation of the Pulmonary Artery. Am. J. Med. 6:24 (Jan.), 1949.

The literature on pure congenital pulmonary stenosis and on idiopathic congenital dilatation of the pulmonary artery is reviewed. The clinical and hemodynamic findings in four additional cases of each of these conditions are reported.

Hemodynamic studies on the eight subjects described by the authors were carried out by the method of cardiac catheterization. Analysis of the oxygen contents of mixed venous and arterial bloods demonstrated the absence of abnormal shunts. It was found that the patients with both pure pulmonary stenosis and simple dilatation of the pulmonary artery demonstrated a significant drop between the systolic pressure in the right ventricle and that in the pulmonary artery. However, the presence of a narrow outlet in patients with pulmonary stenosis caused hypertension in the right ventricle. In simple pulmonary artery dilatation the systolic pressure in the right ventricle was not increased.

SCHWARTZ.

Good, C. A., and Drey, T. J.: Conditions Which Result in Increased Pressure Within the Lesser Circulation. Am. J. Roentgenol. **61**:26 (Jan.), 1949.

Hypertension within the lesser circulation may arise under a variety of circumstances. In certain conditions in which rapid development of pulmonary hypertension occurs, dilatation rather than hypertrophy of the right ventricle takes place. This change is reversible if the cause of the increased pressure is eliminated.

The roentgen signs of pulmonary hypertension are (1) enlargement of the pulmonary arteries and of the outflow tract of the right ventricle (pulmonary conus) and (2) enlargement of the right side of the heart. If incompetence of the pulmonary valve is added, a "hilar dance" may be seen.

The various conditions which cause pulmonary hypertension may be classified in four groups.

(1) *Obstruction beyond the pulmonary system.*—The most common causes are mitral stenosis and a failing left ventricle for any cause.

(2) *Obstruction within the pulmonary system.*—The main vessels may be excluded by an embolus or a thrombotic process. The small and medium-sized branches may become occluded in the course of sickle-cell anemia, schistosomiasis, or carcinomatosis. The arterioles may become sclerotic or undergo obliterative changes in association with many pulmonary diseases. The capillaries may be obstructed in emphysema and in widespread pulmonary fibrosis such as is found in tuberculosis and pneumoconiosis.

(3) *Shunts.*—Abnormal shunts from the arterial side into the lesser circulation are usually congenital but may be acquired. The most common ones are patent ductus arteriosus, interatrial septal defects, and Lutembacher syndrome.

(4) *Kyphoscoliosis.*—This condition probably causes pulmonary hypertension because the thoracic deformity produces areas of atelectasis and of emphysema in the lung.

ZION.

Williams, R. G., and Steinberg, I.: The Value of Angiocardiography in Establishing the Diagnosis of Pericarditis With Effusion. Am. J. Roentgenol. **61**:41 (Jan.), 1949.

The diagnosis of pericarditis with effusion is often difficult. The appearance of the cardiac silhouette on roentgenologic examination is probably the most reliable sign of pericarditis with effusion. Enlargement of the cardiac silhouette, most marked in its transverse diameter, with distortion of the posterior inferior recess and foreshortening of the vascular shadow, most evident with the patient in the recumbent position, and change in size and shape of the cardiac silhouette within a short period of time, can be recognized. These findings are also variable and marked cardiac enlargement will often present the same appearance.

The method of Robb and Steinberg for cardiovascular visualization was used to study four patients in whom the routine methods of investigation were inconclusive in establishing the diagnosis of pericardial effusion. Films were exposed in the posteroanterior projection. In each instance the opacified right and left cardiac chambers were seen to lie well within the cardiac silhouette while the intervening space represented the chamber walls and the fluid within the pericardial sac. Pericardial tap with removal of fluid confirmed the diagnosis in one of these patients.

ZION.

Artz, C. P., Martin, M., and McCleery, R. S.: Disadvantages of Dicumarol With Special Reference to Therapeutic Inadequacies. Am. J. Surg. **77**:47 (Jan.), 1949.

From a study of the problem of venous thrombosis in twenty-four patients, the authors point out some of the pitfalls, difficulties, and reasons for failure of Dicumarol therapy. 1. Too often the unpredictable response of the patient to Dicumarol makes it very difficult to maintain the prothrombin level in the suggested therapeutic range of 10 to 30 per cent of normal. 2. The Dicumarol effect, as evidenced by the Quick prothrombin test, may be most inaccurate if determined on blood containing moderate amounts of heparin. This is due to the effect of heparin on the end point of the test. 3. Thrombosis may occur even when a prophylactic prothrombin depression has been maintained within the therapeutic range. 4. Two patients with thrombosis were observed in whom the thrombotic process extended in spite of a Dicumarol-induced hypo-

prothrombinemia of less than 30 per cent of normal. 5. A transfusion of whole blood and vitamin K therapy necessary to rectify excessive depression of plasma prothrombin by Dicumarol may increase the coagulability of the blood sufficiently to allow thromboembolism to occur.

Although Dicumarol has been the popular anticoagulant in this country for several years, the newer preparations of heparin in a gelatin menstruum may prove safer, more dependable, and just as economical, if one considers the cost of the necessary daily prothrombin test.

BECK.

Prudente, A.: Complete Ligation of the Abdominal Aorta for Aneurysm by the Spiral Method. A Case Controlled by Aortography. Am. J. Surg. **77**:79 (Jan.), 1949.

The author reports the case of a 44-year-old white man with aneurysm of the abdominal aorta and the right common iliac artery in whom ligation of the aorta was performed.

The author feels that the most important factor in the cure of aortic aneurysm is the proximal occlusion of the vessel. The ligature material must be well tolerated by the organism, be pliable, and be of moderate elasticity in order to compress the artery sufficiently. From observation of the case presented the author draws the following conclusions: (1) A fascia lata ligature in spiral form effects total and definitive occlusion of the abdominal aorta. (2) The troubles caused by ligation are neurotrophic due to the deficiency of the blood supply and they gradually disappear. (3) Total and definitive occlusion of the aorta proximal to the aneurysm can effect a cure of the aneurysm.

BECK.

Wright, I. S.: The Use of the Anticoagulants in the Treatment of Diseases of the Heart and Blood Vessels. Ann. Int. Med. **30**:80 (Jan.), 1949.

Analysis of 800 cases of acute myocardial infarction, of which one-half were treated with Dicumarol and the other half managed in the previously orthodox manner, indicates that the mortality rate from coronary thrombosis with myocardial infarction can be reduced 50 per cent The majority of therapeutic failures are considered to be due to inadequate anticoagulant treatment although some failures have occurred in spite of adequate anticoagulant therapy. Serious hemorrhagic complications from anticoagulants are ascribed to one or more of the following: (1) poor prothrombin tests by the laboratory, (2) lack of sufficiently careful thought and supervision by the physician resulting in overdosage, (3) the presence of associated complications such as blood dyscrasias, serious liver disease, serious renal disease, gastrointestinal ulceration, and colitis, and (4) a recent surgical procedure or injury which has not sufficiently healed.

The author also discusses the matter of long term anticoagulant therapy in ambulatory patients for the control of (1) multiple embolic episodes in patients with chronic rheumatic heart disease and auricular fibrillation, (2) persistent migratory phlebitis, (3) recurrent thrombophlebitis including familial thrombo-embolic disease, and (4) recurrent coronary thrombosis associated with myocardial infarction.

Finally, the author, pointing out that current anticoagulant drugs and methods are not altogether satisfactory, lists the requirements which should be fulfilled by the ideal anticoagulant of the future.

WENDKOS.

Schemm, F. R.: Certain Clinical Aspects of the Application of Water Balance Principles to Heart and Kidney Disease. Ann. Int. Med. **30**:92 (Jan.), 1949.

The author stresses the importance of concentrating as much upon the body requirements for plain water as upon the needs for protein and sodium in the therapy of serious illness associated with malfunction of the kidney. The plain water deficit in the very ill often amounts to from 4.5 to 7 liters. Such a deficit results in a degree of cellular dehydration and of extracellular fluid concentration (true dehydration) which is capable of injuring *normal* kidneys or of making *diseased kidneys* worse, or of precipitating a so-called "renal shut-down." The resistant anuria which results and is occasionally irreversible, is usually, but wrongly, attributed entirely to the *inability* of the kidneys to excrete water or salt, while, in the vast majority of instances, it results

from exhaustion of body water and from the diversion of water (and salt) from the kidneys. Studies in the last two decades, particularly of water metabolism and renal function, however, show that: (1) Even badly impaired kidneys *can* excrete all the plain water that reaches them and can excrete the sodium and metabolic solids which reach them if enough water reaches the kidneys to provide them with from 2,000 to 3,000 c.c. of urine-water daily. (2) The vaporization of water for temperature regulation in disease may demand as much as 2,000 to 5,000 c.c. of water before any can reach the kidneys. (3) A pre-existing true dehydration, or plain water deficit, which is often encountered in the presence of edema as well as in its absence, may require for its correction from 4,000 to 7,000 c.c. of water before any reaches the kidneys. (4) Retention of sodium salts, along with an excess of basic ash sufficient to neutralize the metabolic acids, results in the diversion of water to edema formation in amounts that might otherwise be adequate for the needs of the body. (5) Extra acid sodium salts and nitrogenous wastes, in the presence of an insufficient supply of water, are eliminated in urine water derived from the expendable fraction (4,000 to 7,000 c.c.) of the 50 liters of body water, almost three-fourths of this water coming from the cells. The resultant cell dehydration seems to be more harmful to the cells of the body than either edema or azotemia. With rehydration and a large volume of urine water, mercurial diuretics can be used safely in nephritis and often with great benefit, whereas with an inadequate water supply they may induce evidence of renal injury in patients with originally normal kidneys. In the most resistant cases however, a good output of urine water, with an adequate restriction of sodium and the use of mercurials, may be ineffective in clearing edema until enough acid is supplied to augment the action of the metabolic acids and "mobilize" sodium.

By means of illustrative cases, the author demonstrates the value of these principles when applied to the correction of disturbed renal function associated with acute myocardial infarction, protracted vomiting, acute hemorrhagic nephritis, and chronic glomerular-nephritis with the nephrotic syndrome.

WENDKOS.

Scherf, D., Silver, A. M., and Weinberg, L. D.: Clinical Observations With Fagarine. Ann. Int. Med., **30**:100 (Jan.), 1949.

Alpha-fagarine hydrochloride, an alkaloid derived from the Argentinian plant *Fagaro coco*, was administered by intramuscular injection to thirteen patients whose ages ranged from 45 to 94 years. Only a single injection was employed and the dosage averaged slightly less than 2.0 mg. per kilogram of body weight. Electrocardiograms were made just prior to the injection, at frequent intervals for a two-hour period afterward, and repeatedly during the follow-up period in the hospital. Normal sinus rhythm was restored for varying lengths of time in three patients with auricular fibrillation and in two patients with auricular flutter. However, because of the relatively frequent occurrence of ventricular extrasystoles and ventricular fibrillation in their series of patients the authors do not recommend fagarine for the treatment of heterotopic auricular arrythmias. The development of the ventricular arrythmia did not seem to bear any relationship to the dosage of the drug. Other effects included lengthening of the Q-T interval, depression of the RS-T segment, and diminution of the amplitude of the T wave.

WENDKOS.

Nichols, E.: Transient Right Bundle Branch Block, Wide S-Wave Type, in Which Normal Conduction Occurred Both Spontaneously and in Response to Vagal Stimulation. Ann. Int. Med., **30**:196 (Jan.), 1949.

A 28-year-old soldier presented an electrocardiogram which revealed the wide S pattern of right bundle branch block. Because of this finding electrocardiographic studies, employing specialized techniques were made on nine separate occasions. It was observed that normal intraventricular conduction was temporarily restored during breath holding maneuvers, during the eight to fifteen minute period following the subcutaneous administration of 1.5 mg. of atropine sulphate, and during left carotid sinus pressure. Postural changes, continuous inhalation of high concentrations of oxygen, the inhalation of amyl nitrite, the intramuscular injection of 2.5 mg. of Prostigmine, and the intramuscular injection of 0.5 mg. of ergotamine tartrate did not

modify the abnormal electrocardiographic pattern even though the last named procedure resulted in considerable cardiac slowing. Spontaneous reversion to normal intraventricular conduction during some of the cardiac cycles in a routine clinostatic electrocardiogram was observed only once. The occurrence of normal and abnormal complexes could not be related to the heart rate. The author infers, on the basis of his studies, that the bundle branch block in this particular case may be the result of interference with normal intraventricular conduction because of overstimulation of sympathetic nerves which supply the bundle branches.

WENDKOS.

Curtis, A. C., and Horne, S. F.: Disseminated Lupus Erythematosus With Pericardial Effusion. Ann. Int. Med., **30**:209 (Jan.), 1949.

Polycyclic migratory polyarthritis, intermittent fever, skin lesions of lupus erythematosus, and the relatively rapid development of cardiac enlargement were observed in two young women who came to the attention of the authors. Both patients eventually died from convulsive seizures after renal and cardiac function became progressively impaired. In the first patient, it was considered that a massive pericardial effusion was responsible for the cardiac enlargement although pericardial paracentesis was not performed during life. An autopsy was not done. In the other patient, repeated pericardial paracentesis was performed and large amounts of fluid were removed each time. In this patient, too, an autopsy was not allowed. On the basis of their experience with these two patients, the authors emphasize the need for considering disseminated lupus erythematosus as a possible cause in any case of pericarditis with large quantities of effusion.

WENDKOS.

Gersten, J. W., Wakim, K. G., Herrick, J. F., and Krusen, F. H.: The Effect of Microwave Diathermy on the Peripheral Circulation and on Tissue Temperature in Man. Arch. Phys. Med. **30**:7 (Jan.), 1949.

Using skin and muscle thermocouples and the venous occlusion plethysmograph, the authors attempted to study the changes in peripheral circulation of fifty normal human subjects produced by exposure of the limbs to microwave diathermy.

It was concluded that the amount of energy absorbed by muscle with this procedure was greater than that absorbed by subcutaneous tissue or skin. This view was based on the finding of greater rises of temperature in muscular tissue one minute after the microwaves had been turned off than was observed in the other tissues. The fact that the conductivity of muscle is greater than that of fatty tissue was presented as a possible explanation for the observation. During the second minute after the microwaves had been turned off the fall of temperature of subcutaneous tissue was greater than that of either muscle or skin. It was believed that the low specific heat of subcutaneous tissue might have been a contributing factor to the observed response.

Significant increases in blood flow and tissue temperature were noted with 60 and 80 watt exposure and with all the durations used.

ABRAMSON.